

# Sentinel Site–Based Pilot Active Surveillance Pharmacovigilance in the Vietnam ART Program

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and the  
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## **About SPS**

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

## **Key Words**

active surveillance, adverse drug reactions, antiretroviral therapy, pharmacovigilance

Strengthening Pharmaceutical Systems  
Center for Pharmaceutical Management  
Management Sciences for Health  
4301 North Fairfax Drive, Suite 400  
Arlington, VA 22203 USA  
Telephone: 703.524.6575  
Fax: 703.524.7898  
E-mail: [sps@msh.org](mailto:sps@msh.org)  
Web: [www.msh.org/sps](http://www.msh.org/sps)

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## ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
ADR	adverse drug reaction
AE	Adverse event
ART	antiretroviral therapy
ARV	antiretroviral medicine
AZT	zidovudine
CD4	cluster of differentiation found on a subset of T-lymphocyte
D4T	stavudine
DAV	Drug Administration of Vietnam
DI&ADR Center	National Drug Information and Adverse Drug Reaction Monitoring Center
DTC	Drug and Therapeutics Committee
EFV	efavirenz
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HAART	highly active antiretroviral therapy
HCMC	Ho Chi Minh City
IT	Information technology
MSA	Medical Services Administration
NVP	nevirapine
OPC	outpatient clinic
PAC	Provincial AIDS Committee
PV	pharmacovigilance
SPS	Strengthening Pharmaceutical Systems (Program)
TB	Tuberculosis
TDF	tenofovir
VAAC	Vietnam Administration of AIDS Control
WHO	World Health Organization



## SUMMARY

Proposed is a pilot system for monitoring the safety and tolerability of antiretroviral therapy (ART) at sentinel sites in Vietnam through sentinel site active surveillance. It aims to develop, implement, and demonstrate the local feasibility of a practical and sustainable pharmacovigilance system that could later be scaled up to monitor the safety of antiretroviral medicine (ARV) regimens across Vietnam. It also has applicability for future active surveillance of other medicines, settings, and populations. The active surveillance activity, developed in consultation with stakeholders, proposes to systematically document and quantify the presence or absence of ARV-related adverse events and to determine risk factors at three sentinel sites in Vietnam. For this pilot activity, it is proposed that the active surveillance be initiated and evaluated at three outpatient ART health care facilities, two in Ho Chi Minh City (HCMC) and one in Hanoi. Systematically collecting information about medicines used in a defined population can help ensure that medicines have an acceptable safety profile and are used safely.



## OVERALL GOAL AND SPECIFIC AIMS

### Overall Goal

The overall goal of this proposed activity is to implement and evaluate a pilot pharmacovigilance active surveillance at three sentinel sites in Vietnam's ART program to generate local, evidence-based information to improve the systematic identification, diagnosis, management, and prevention of medicine-related morbidity and mortality in HIV-infected patients on highly active antiretroviral therapy (HAART).

### Specific Aims

1. Develop, implement, and field-test procedures and tools for sentinel site active surveillance of ARTs.
2. Prospectively determine the incidence of and risk factors for suspected adverse drug events in treatment-naïve adults receiving HAART at sentinel site ART clinics.
3. Evaluate the pilot program and demonstrate the feasibility of using active surveillance as a sustainable platform for assessing the safety and use of HAART to help support evidence-based decision making, including review of standard treatment guidelines.



## BACKGROUND AND RATIONALE

The government of Vietnam launched its National Drug Information and Adverse Drug Reaction Monitoring Center (DI&ADR Center) to strengthen pharmacovigilance activities in the country. Under the Rational Pharmaceutical Management Plus Program, Management Sciences for Health assisted the government of Vietnam and its partners in developing a framework for medication safety and pharmacovigilance that acknowledged the importance of active surveillance methods in support of public health programs, including the use of sentinel sites and follow-up of patient cohorts. This one-day national stakeholder consensus meeting held on March 25, 2009, was followed by a three-day training-of-trainers Introduction to Pharmacovigilance course for staff from public health programs and other key institutions. Since that time, the Vietnam Administration of AIDS Control (VAAC) and the DI&ADR Center, Hanoi University of Pharmacy, have expressed interest in initiating a pilot active surveillance activity within the ART program. In July 2009, the Strengthening Pharmaceutical Systems (SPS) Program, which is a follow-on to Rational Pharmaceutical Management Plus, made a technical support visit to the center's staff to draft a one-year work plan and to develop a strategy for including pharmacovigilance activities in a proposal to the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). SPS subsequently provided further technical assistance to strengthen the capacity of the newly established center's staff to carry out drug information and pharmacovigilance activities. Building on these foundations, SPS has collaborated with VAAC and the DI&ADR Center and has obtained inputs from other stakeholders to develop this draft protocol for pilot active surveillance activity within the ART program in Vietnam.

### The Need for Pharmacovigilance of Antiretroviral Medicines

According to the World Health Organization (WHO), *pharmacovigilance* is the science and activities relating to the detection, evaluation, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems.<sup>1</sup> Despite their lifesaving and quality-of-life-improving effects, ARVs are associated with safety issues ranging from minor to more serious adverse drug reactions (ADRs), with both short- and long-term effects.<sup>2</sup> Major adverse events associated with the use of ARVs affecting patient adherence and outcomes include lipodystrophy, anemia and neutropenia, hypersensitivity reactions, hepatic disorders, acute pancreatitis, osteopenia and osteoporosis, and lactic acidosis.<sup>3</sup> However, little is known about the epidemiology of the toxicity profiles of ARVs in low- and middle-income countries, despite the

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<sup>1</sup> World Health Organization. 2002. *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products*.

<sup>2</sup> World Health Organization. 2006. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 Revision*. Geneva: WHO. <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>.

<sup>3</sup> Vietnam HIV/AIDS Treatment Guidelines (Part A: Diagnosis and Treatment of HIV/AIDS in Adults; Part B: Diagnosis, Treatment and Care for HIV/AIDS-infected Children).

importance of such information for regulatory and public health decision making.<sup>4</sup> These countries have special factors and different, and medicine use and its safety may therefore vary considerably, including the presence of conditions such as tuberculosis (TB), malnutrition, reliance on traditional or alternative therapies, and likelihood of medicine interactions.<sup>5</sup> ADRs are among the most important factors interfering with patient adherence to ART, thus monitoring and managing adverse reactions to ARVs is important.

## **Active Surveillance as a Tool for Pharmacovigilance within Public Health Programs**

With expanded access to ARVs, recognition of the need to implement systematically conducted pharmacovigilance activities within public health programs is increasing.<sup>6</sup> Linking and coordinating national pharmacovigilance activities with in-country public health programs supports overall system strengthening and can help achieve better program outcomes. The conduct of surveillance—that is, ongoing systematic collection, analysis, and interpretation of data—is not a new concept for HIV/AIDS programs.<sup>7</sup> As a tool for pharmacovigilance, active surveillance involves methodically searching for exposures and health outcomes, often at sentinel site facilities.<sup>8</sup> It consists of the systematic collection, analysis, interpretation, and dissemination of data regarding one or more medicine-related outcomes using observational methods.<sup>9</sup> Through active surveillance, potential safety problems and their risk factors can be identified for specific populations of patients. Systematically collecting information about medicines used in a defined population can help ensure that medicines have an acceptable safety profile and that they are used safely. It also helps understand the scope of ADRs. Because these methods involve obtaining a denominator of persons exposed to medications of interest, calculation of rates of adverse drug events is possible.

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<sup>4</sup> Modayil, R. R., et al. 2010. Adverse Drug Reactions to Antiretroviral Therapy (ART): An Experience of Spontaneous Reporting and Intensive Monitoring from ART Centre in India. *Pharmacoepidemiology and Drug Safety* 19(3): 247–55. doi: 10.1002/pds.1907.

<sup>5</sup> Pirmohamed, M.,K. N. Atuah, A. N. Dodoo, and P. Winstanley. 2007. Pharmacovigilance in Developing Countries. *BMJ* 335(7618): 462.

<sup>6</sup> World Health Organization. 2007. *A Practical Handbook on the Pharmacovigilance of Antimalarial Medicines*. Geneva: WHO. <http://www.who-umc.org/graphics/19449.pdf>.

<sup>7</sup> U.S. Agency for International Development. Facility-Based Routine Surveillance. [http://www.usaid.gov/our\\_work/global\\_health/id/surveillance/fbrsurveillance.html](http://www.usaid.gov/our_work/global_health/id/surveillance/fbrsurveillance.html) (Last Updated on: June 02, 2009).

<sup>8</sup> Strengthening Pharmaceutical Systems (SPS). 2009. *Supporting Pharmacovigilance in Developing Countries: The Systems Perspective*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

<sup>9</sup> U.S. Centers for Disease Control and Prevention. 2001. Updated Guidelines for Evaluating Public Health Surveillance Systems: Recommendations from the Guidelines Working Group. *MMWR Recommendations and Reports* 50(RR13): 1–35. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5013a1.htm>.

The importance of active surveillance as a systematic approach to medicine safety assessment and pharmaceutical systems strengthening has been cited by many in the field.<sup>10,11,12</sup> An increasing number of low- and middle-income countries are establishing active surveillance methods for ARVs and other medicines important to public health programs. In 2007, the Tanzania Ministry of Health and Social Welfare, Tanzania Food and Drugs Authority, initiated a cohort event monitoring study of adverse reactions among users of ARVs in Tanzania. Beginning in August 2007, USAID–U.S. President’s Malaria Initiative supported a pilot pharmacovigilance system for antimalarials in Jinja, Uganda. More recently, the KwaZulu Natal Department of Health in South Africa received funding from the Global Fund to support the further development of pharmacovigilance activities in the province, including a provincial cohort event monitoring program intended to collect long-term data on safety and treatment outcomes in ART patients at eight sentinel sites in the province. In addition, a record-linking active surveillance activity is under way in Namibia on the association between zidovudine and the risk of anemia. Active surveillance can provide accurate and timely information for program and guideline development or change. Moreover, an active surveillance system will increase reporting of potential ADRs, thereby strengthening spontaneous reporting approaches to pharmacovigilance.

### **Sentinel Site Active Surveillance**

*Sentinel surveillance* is the collection and analysis of data by designated institutions selected for their geographic location, medical specialty, and ability to report high-quality data. For example, district hospitals may be required to report specific conditions to quantify the burden of disease. Sentinel sites are often those facilities where pilot programs operate. Such sites are chosen based on certain functions and criteria that are highly relevant for a planned task. Considerations may include representativeness, ease of access, infrastructure support, reasonable patient flow; interest and commitment of the potential site; any ADR-related initiative or expertise already in existence; past performance; level of computerization of ART and patient-related data management; and quality assurance measures in place. Generally, sentinel surveillance is very useful for answering specific questions, but because sentinel sites may not represent the general population or the general incidence of disease, it may have some limitations in generalizing for national disease patterns and trends.<sup>13</sup> Nevertheless, for new surveillance programs, sentinel site strategies are often chosen so that data are manageable in volume and concept and for logistical efficiency, as is the case in the active pharmacovigilance examples previously cited in this proposal (i.e., Tanzania, Uganda, and South Africa). Sentinel site surveillance has the following

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<sup>10</sup> Platt, R., L. Madre, and R. Reynolds. 2008. Active Drug Safety Surveillance: A Tool to Improve Public Health. *Pharmacoepidemiology and Drug Safety* 17(12): 1175–82. doi: 10.1002/pds.1668.

<sup>11</sup> Wise, L., J. Parkinson, J. Raine, et al. 2009. New Approaches to drug Safety: A Pharmacovigilance Tool Kit. *Nature Reviews Drug Discovery* 8(10): 779. doi:10.1038/nrd3002.

<sup>12</sup> World Health Organization. 2007. *A Practical Handbook on the Pharmacovigilance of Antimalarial Medicines*. Geneva: WHO. <http://www.who-umc.org/graphics/19449.pdf>.

<sup>13</sup> USAID. Sentinel Surveillance. [http://www.usaid.gov/our\\_work/global\\_health/id/surveillance/sentinel.html](http://www.usaid.gov/our_work/global_health/id/surveillance/sentinel.html).

additional advantages: regular supervision, feedback, and logistical support can be provided because sentinel sites are located in fewer facilities; higher-quality data can be obtained from a few sites with intensive support of training, supervision, and logistics; and sentinel surveillance systems are less expensive to run and maintain than universal reporting systems.

### **Bridging the Gap: Generating Local Data to Inform Regulatory Actions, Treatment Guidelines, and Care Delivery**

The optimal methodology for drug safety surveillance in resource-limited settings is likely to vary from site to site, but in general, the options are driven by the choice and assessment of outcomes of interest and the methods needed to reliably capture drug exposures. Toward this end, this pilot will make important contributions in terms of the choice and feasibility of data collection methodologies. The data collection tools developed and validated should be applicable to future expansions of active surveillance to other medicines, settings, and population groups as well as support future proposals addressing pharmacovigilance issues. A clear and growing need exists to understand better the benefits and risks of medicines under conditions of actual use. Most questions of drug safety can be answered only by observing and analyzing the use and outcomes of therapy in large populations during the postapproval phase.<sup>14,15</sup> The targeted pharmacovigilance approaches adopted in this proposal will contribute to the knowledge base on this important matter and help develop in-country infrastructure for future active surveillance approaches. In addition to its methodological contribution, this project's results should help inform future revisions of in-country HIV/AIDS treatment guidelines and regulatory decisions. The proposed prospective, observational approach will contribute data to provide estimates of safety of ARVs as well as to conduct a pilot project involving the identification of signals and to evaluate suspicions of risk to provide for better estimates of benefit-risk profiles. In addition, from a patient care perspective, knowledge of factors that may affect the risk and management of adverse reactions, including other illnesses and conditions, the patient's other current medications, the availability of alternative regimens, and the patient's history of medication intolerance, can lead to improved outcomes.

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<sup>14</sup> Committee on the Assessment of the US Drug Safety System. 2006. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Washington, DC: Institute of Medicine.

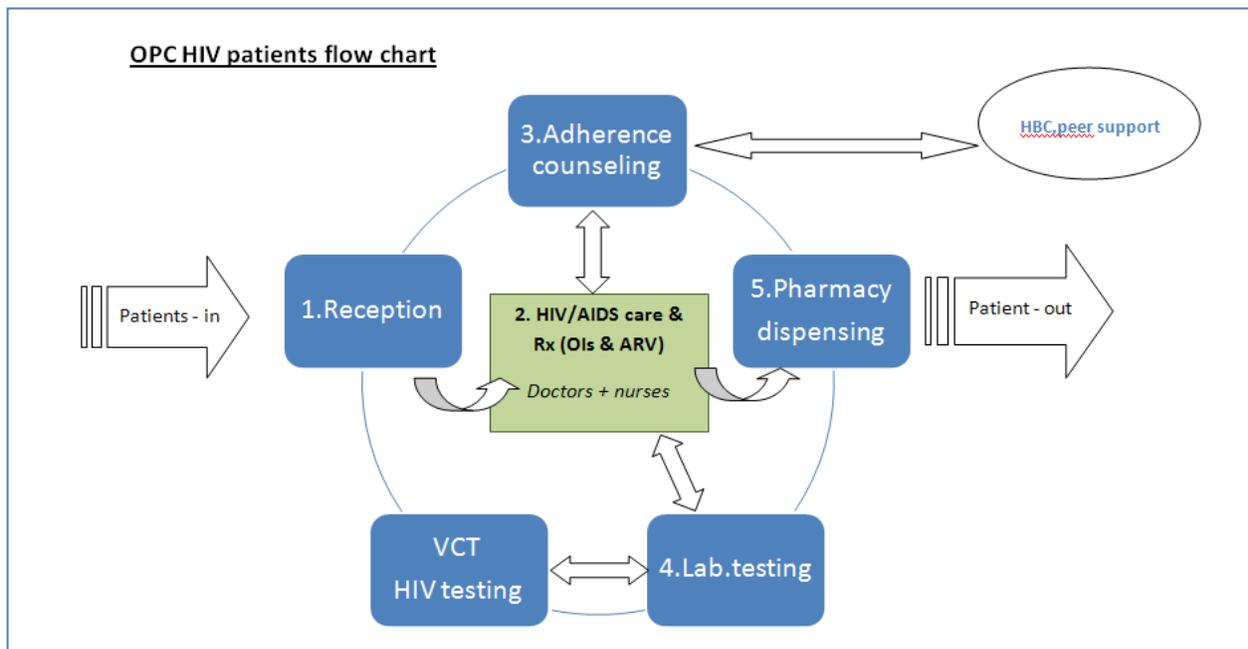
<sup>15</sup> Lang, T., D. Hughes, T. Kanyok, J. Kengeya-Kayondo, V. Marsh, et al. 2006. Beyond Registration—Measuring the Public-Health Potential of New Treatments for Malaria in Africa. *Lancet Infectious Diseases* 6: 46–52.

## METHODS

### Sentinel Sites

Based on the mapping of services and data recording in ART clinics and site visits (figure 1), the initial pilot program is proposed for implementation in three ART outpatient clinics (OPCs) that will serve as the sentinel sites—two clinics in Ho Chi Minh City and one in Hanoi. The proposed sites represent the following different levels of care delivery within Vietnam—

- National level: national HIV/AIDS treatment facilities
- Provincial level: general hospitals
- District level: district-level health centers, which are the central point where comprehensive medical services are provided for persons with HIV/AIDS



Note: HBC = home-based care; OIs = opportunistic infections; VCT = voluntary counseling and testing.

**Figure 1. General overview of OPC HIV patient flow in Vietnam**

Table 1 describes selected characteristics of three sites that were visited during the ART care and mapping process to help inform the development of this protocol. This table shows some key characteristics relevant for the selection of the pilot sites, such as geographical location of the facility, number of key health care staff involved in ART, and average monthly number of patients who meet the suggested inclusion criteria. The sites shown in table 1 are displayed for

illustrative purposes only; the final decision regarding selection of the actual sites for the pilot rests with the VAAC.

**Table 1. Characteristics of Three Sites, One or More of Which Could Serve as Sentinel Sites for the Pilot**

<b>Characteristics</b>	<b>Dong Da Hospital OPC</b>	<b>Tropical Disease Hospital OPC</b>	<b>Binh Than OPC</b>
Geographical location	Hanoi	HCMC	HCMC
<b>Staff</b>			
Clinician	4	7	4
Pharmacist	2	4	2 (pharmacy dispensers)
Nurse	5 (2 also do computer work)	8	2
Information technology staff	2 (nurses)	2	1
Average number of new (treatment-naive) adult ART patients per month	15	90	30
Presence of automated records	Yes	Yes	Yes

## **Data Sources**

Proposed is a data collection strategy that relies mainly on abstracting and recording of sources of data that are already contained in the clinical records of patients who are newly placed on HAART. ARV treatment, and collecting and recording of patient information in Vietnam is conducted in accordance with Ministry of Health guidelines and protocols. For example, the treatment protocol for people living with HIV/AIDS specifies that information should be collected about medical history, clinical stage, side effects and interactions of prescribed medicines, and diagnosis of other diseases, including laboratory tests where indicated. A detailed schedule of follow-up visits is also specified as are provisions for assessing and promoting treatment adherence and treatment effectiveness. Specifically, information from the following *existing data sources* from the sentinel sites will be used for this activity—

- Pre-ART Register and ART Register
- Outpatient Record

One *new data collection form* is proposed for use by the sentinel sites to systematically abstract and record information for this active surveillance activity. The form is designed to be completed by a health care provider when he or she sees the patient. It is intended to capture information on baseline status and on medication and adverse events during start-up of therapy and subsequent follow-up visits through active questioning and recording performed by the attending health care providers. Table 2 lists the suggested minimum data set for this active surveillance activity that

guided the development of the proposed data collection form. The form is included as Annex 3. The first section of the form, designated as Part A, is for recording baseline information before ART is initiated. The second section of the form, designated as Part B, is for recording ART regimens as well as suspected adverse event–related information from ART start through each follow-up visit of the patient to the outpatient clinic.

**Table 2. Minimum Data Set for the Proposed Active Surveillance Pharmacovigilance Pilot**

Type	Variable(s)	Currently Recorded?	Comment
Patient data	Unique patient ID number	Yes	Necessary for record linkage
	Assigned code number	No	Can be used if concerns about confidentiality exist
	Contact details	Yes	Including treatment supporter if available
	Age/date of birth, gender, weight/height (BMI), pregnant, other notable conditions	Yes	Routinely recorded in the Outpatient Records and Pre-ART and the ART Register
Medicine exposure data	ARV drug name, strength, dose	Yes	Contained in Outpatient Record and ART Register
	Date ARV initiated and stopped	Yes	Contained in Outpatient Record and ART Register
	Adherence to ARV	Yes	Contained in the Checklist for Adherence Assessment During Treatment and the Outpatient Record
	Concomitant medications	Yes	Contained in Outpatient Record and ART Register
Outcome data	Adverse drug event and outcome	Yes	Recorded; however, will need to be recorded more systematically for active surveillance
	Classifications of seriousness and severity of outcome	No	New information needed to be collected for active surveillance
	Effect of challenge/rechallenge if applicable	No	New information needed to be collected for active surveillance
	Laboratory values	Yes	Only selected laboratory tests are to be recorded on the form

### **Selection of Patients**

The inclusion and exclusion criteria for patient enrollment in this active surveillance activity are specified below.

- *Inclusion criteria:* adult treatment-naive HIV/AIDS patients (older than 16 years of age) who attend clinic and are enrolled for ART initiation

- *Exclusion criteria:* pediatric and adolescent HIV/AIDS patients and treatment-experienced adult HIV/AIDS patients (i.e., those persons with previous or currently ongoing treatment with ARVs)

## **Patient Outcomes**

The following outcomes should be recorded on the Active Surveillance Form: suspected ADRs and other selected adverse events (AEs), such as hospitalization, death, and suspected therapeutic failure. Clinicians or other recording health care staff should be asked to make no judgment on causality, and normal clinical terms or descriptions should be used. Specifically, health professionals will be asked to record the following types of events—

- All *new AEs* even if minor
- Abnormal *changes* in laboratory tests compared with a previous examination
- Suspected lack of *effectiveness*
- *Admission to hospital* with date and cause
- The first observation of *pregnancy* of any duration
- All *deaths* with date and cause
- Possible *drug interactions*

## **Duration of Surveillance and Duration of Pilot Activity**

Because this is a pilot project, an 18-month follow-up for each person recruited into the active surveillance is proposed. The three sentinel sites suggested as examples in table 1 have the potential for recruiting at least 500–600 adult treatment-naïve HIV/AIDS patients over a four- to six-month period. The cohort recruitment at each sentinel site is proposed to continue until a predefined patient number for that site is reached. Selection of sites that receive higher number of new ART-naïve adult patients is likely to help hit the required target number more quickly. For example, given their average numbers reported to date, the three suggested sentinel sites could recruit up to 135 new ART-naïve adult patients per month, with a busy OPC such as the Tropical Disease Hospital accounting for two-thirds of that total.

Each recruited patient will be followed from the start of ART for 18 months, and data updates will be requested from sentinel sites on a quarterly basis. It is expected that active surveillance information will be integrated into usual care and collected every time the patient comes for follow-up, which typically is once a month for stabilized patients. The standard practice at the ART OPCs includes efforts made to track patients who do not present for follow-up visits. For the overall pilot activity, a period of about 28 months is proposed, commencing upon receipt of necessary approvals. The overall proposed period accounts for a 1-month training at the beginning of the activity and a 3-month analysis and reporting period at the end of the activity. It also allows at least 18 months of follow-up for every patient recruited into the active surveillance.

## Data Entry and Analysis

Data entry will be done using a simple database. As data accumulate, descriptive frequency tables for demographics, medicine use, and adverse drug events will be presented periodically. As the program matures and more data accumulate, statistical analysis will be performed to understand and present various AE profiles, such as incidence rates, predictors of adverse events, and relative risks. Frequencies and risks of adverse drug events will be compared by medicine category. Multivariate models will be developed to identify predictors of adverse drug events, taking into account potential confounders (table 3).

The incidence rate of an event will be calculated as the number of events divided by the total number of patient-months of follow-up, that is, for ADRs by type. Estimates will be given with 95 percent confidence intervals assuming a Poisson distribution. Regression models will be used to investigate factors associated with the occurrence of the endpoint events.

**Table 3. Variables to Be Used in Analyses**

<b>Variable Name</b>	<b>Category</b>	<b>Type</b>
HAART regimen	Primary exposure	Categorical
Age	Confounder	Continuous
Gender	Confounder	Binary; male or female
Baseline CD4	Confounder	continuous
Baseline hemoglobin	Confounder	Continuous
Baseline co-illnesses	Confounder	Categorical
Co-trimoxazole use	Confounder	Binary; yes, no
Baseline comorbidities	Confounder	Categorical
Duration of HAART	Effect modifier	Continuous

One of the goals of the surveillance program is to link itself with WHO resources and participate in the Uppsala Monitoring Center global safety surveillance support and at the same time derive benefit from a supranational global network.

## Sample Size Estimation

A cohort of approximately 500 to 600 persons on ART gives a 99 percent chance of identifying an adverse drug event that is expected to occur with an incidence of 1:100 and a 92 percent chance of identifying an adverse drug event occurring at a rate of 1:200 persons in one of the ART groups. As table 4 shows, larger sample size increases the likelihood of identifying less common AEs. However, detecting rare adverse drug events requires sample sizes beyond the scope of this pilot project. The key objective of the pilot is to demonstrate feasibility of the program, which will help in scaling up the program in future, thus leading to larger sample sizes that help in detecting less common adverse drug events. Besides providing information on such

feasibility issues, the proposed pilot will help characterize AEs that are commonly encountered in terms of their incidence and risk factors.

**Table 4. Relationship between Sample Size and Probability of Observing an AE: Percent Probability of Observing at Least One AE in the Sample by AE Expected Incidence**

<b>Expected AE Incidence: 1 Event out of ... Patients</b>							
<b>Sample Size</b>	<b>100</b>	<b>200</b>	<b>500</b>	<b>1,000</b>	<b>2,000</b>	<b>5,000</b>	<b>10,000</b>
200	86.47	63.21	32.97	18.13	9.52	3.92	1.98
300	95.02	77.69	45.12	25.92	13.93	5.82	2.96
500	99.33	91.79	63.21	39.35	22.12	9.52	4.88
700	99.91	96.98	75.34	50.34	29.53	13.06	6.76
1,000	100.00	99.33	86.47	63.21	39.35	18.13	9.52

Source: WHO. 2009. *A Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines*.

## QUALITY CONTROL OF DATA AND TRAINING

Training needs to be defined and provided. Topics to be covered include defining AEs and ADRs and the purpose of pharmacovigilance and the pilot surveillance system. Emphasis will be placed on what to report and how to report using the pilot system.

Training sessions will be provided at the outset of the pilot to all key members of the sentinel sites, the VAAC, Provincial AIDS Committee (PAC), DI&ADR Center, and Pharmacovigilance (PV) Technical Committee. The active surveillance forms will be pretested and modified accordingly, including the precoded options on the form. To ensure credibility of results generated as part of the pilot, quality assurance tools such as standard operating procedures will be implemented.

The training of personnel at all sites will be performed before the initiation of the activity. Quality assurance procedures will also include at least annual visits to the participating sites by a designated monitor from VAAC, PAC, or DI&ADR Center. Site monitoring will include a review of a sample of source documents.



## APPROVAL, DATA CONFIDENTIALITY, AND ETHICAL CONSIDERATIONS

The VAAC and Hanoi University of Pharmacy/DI&ADR Center will need to determine an approval process and obtain or provide a formal approval to initiate the pilot. This will be an observational activity with minimal risk where the information is collected from the patient and from the clinical history of the patient without any intervention. All patient identifiers will be encrypted. Procedures will be established and maintained to ensure the confidentiality of data and unauthorized persons will not have access to the data. Regarding these issues, the WHO 2009 *Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines* (85–87) writes—

Because it is essential to record personal identifiers, the security, privacy and confidentiality of personal data need to be strenuously maintained...should avoid attempting to obtain individual informed consent if at all possible because it will be time-consuming to try to explain the concepts of pharmacovigilance to each patient, will increase complexity and add to the cost, and could potentially compromise the validity of the results if many patients refuse to be enrolled. [It] is not a clinical trial or research study and does not interfere with treatment in any way. It is simply a process of observation data collection in the interests of public health.



## **LIMITATIONS**

The proposed activity has some limitations. For example, the duration of patient follow-up for this prospective study is limited to 18 months. Additionally, the geographic coverage of the sentinel sites is limited and cannot be generalized to the entire country of Vietnam.



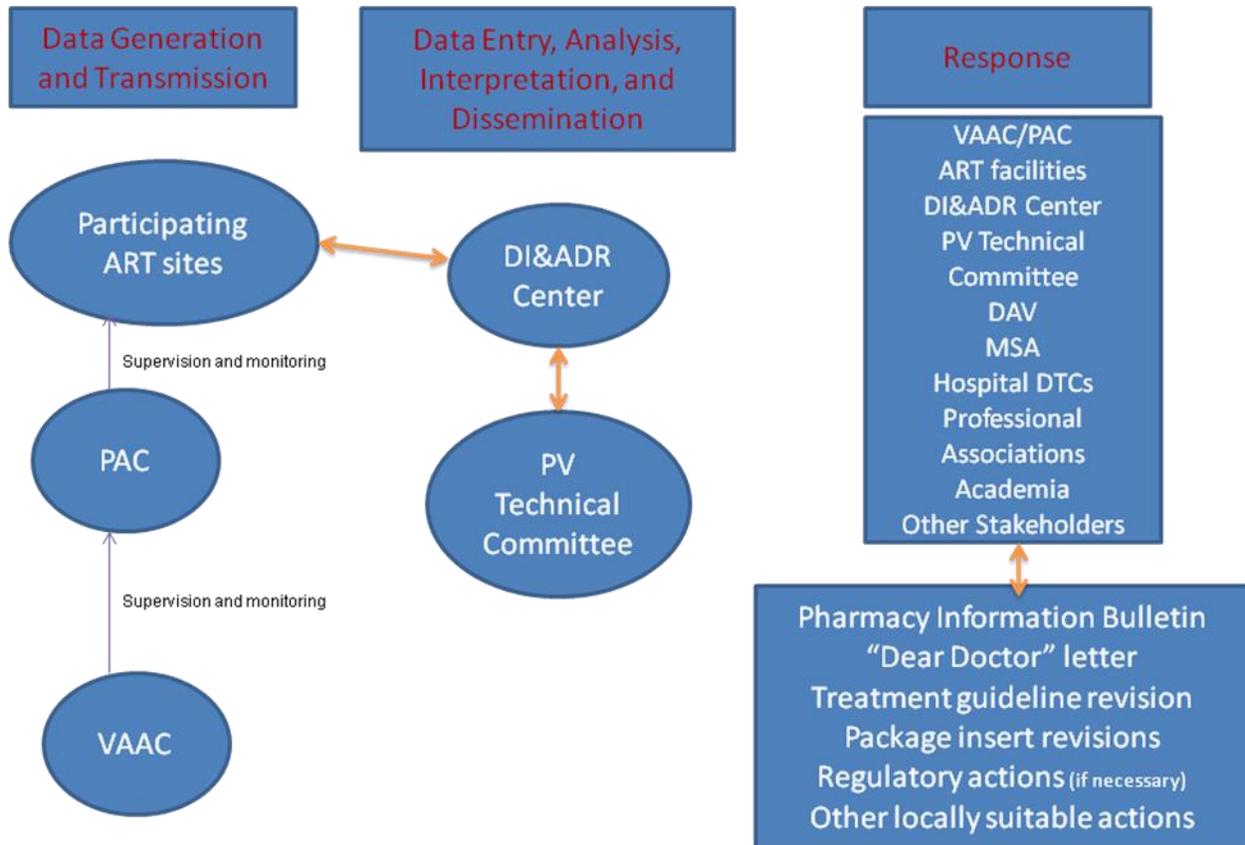
## **SUGGESTED FRAMEWORK OF THE PILOT ACTIVITY AND ROLES AND RESPONSIBILITIES OF KEY STAKEHOLDERS**

### **Suggested Framework**

The suggested framework envisages an intersectoral surveillance system that functions in a coordinated manner to (a) generate data, (b) analyze and interpret data, and (c) create locally appropriate responses based on the data. As figure 2 depicts, the sentinel ART sites generate data, and the DI&ADR Center analyzes and interprets the data, leading to concerted responses by several pharmacovigilance stakeholders. The framework links the ART public health program group (VAAC, PAC, and ART sites) with the national pharmacovigilance center (DI&ADR Center), which is a highly desirable mechanism for building an interconnected and strong pharmacovigilance system.

### **Suggested Information Flow within the Sentinel Sites**

This section contains a suggested flow of information within sentinel sites from a patient's and a health care worker's perspective. When new ART-naïve adult patients arrive at an OPC for the first time, the receptionist begins the process by filling out Part A of the Active Surveillance Form (Annex 3), primarily using patient information that is already included in the Registration Sheet for Enrollment in HIV/AIDS Care and Treatment Program form. Immediately following the initial visit, the Initial Visit section of the Outpatient Record is reviewed, and essential data elements for active surveillance are abstracted onto the Active Surveillance Form, preferably by a nurse. At follow-up visits, the physician or other clinical officer is requested to complete Part B of the Active Surveillance Form for each follow-up visit, indicating, for example, the presence or absence of adverse drug events. An information technology (IT) person on site then enters Active Surveillance Forms into a computer and transmits the data electronically from sentinel sites to the DI&ADR Center in accordance with prespecified intervals, for example, every three months. Alternatively, a copy of the Active Surveillance Forms can be transmitted to the DI&ADR Center manually.



**Figure 2. Suggested framework for pharmacovigilance active surveillance pilot in the ART program in Vietnam**

### Suggested Roles and Responsibilities

Roles and responsibilities of the various stakeholder groups for the pilot are suggested below and summarized in the box. These active surveillance–related roles were aligned as much as possible with their existing roles and functions.

- Each sentinel site fills out the active surveillance form for each recruited ART-naive adult patient planned for ART. The form is filled when the ART is being initiated and subsequently thereafter during each follow-up visit. The sentinel site also transmits data quarterly to the DI&ADR Center (preferably via e-mail) and a brief summary report quarterly to the PAC in a standardized format.
- The PAC supports, supervises, and monitors compliance of ART sites with filling in the active surveillance form and transmitting the data quarterly to the DI&ADR Center.
- The VAAC provides supportive supervision to the PAC for its supervision and monitoring role.

- The DI&ADR Center acknowledges each time it receives reports from ART facilities, files the received forms (ensuring strict data confidentiality), enters the information into the database, assesses causality, and disseminates summary reports periodically to several stakeholders. It sends reports to the VAAC, the PAC, the PV Technical Committee, participating sentinel sites, the Medical Services Administration (MSA), and the Drug Administration of Vietnam (DAV) every three months. It also disseminates summary reports to professional associations, training institutes, hospital Drug and Therapeutics Committees (DTCs), and other identified key stakeholders, including WHO and other development partners, at least annually.
- The Ministry of Health's PV Technical Committee provides expert advice and guidance to the DI&ADR Center on causality assessment and other technical issues.
- The VAAC, PAC, PV Technical Committee, DI&ADR Center, MSA, DAV, hospital DTCs, professional associations, and other stakeholders collaborate to generate data-driven and evidence-based locally appropriate actions such as reports and articles in the Pharmacy Information Bulletin and other publications; drug alerts and other communications to health care workers and the patients or public; treatment guideline revisions; package insert revisions; regulatory actions, if necessary; and other locally suitable actions.

**Box. Responsibilities of Stakeholders for Active Surveillance Pilot**

**ART Facilities**

- Part A of Form: Completed by receptionist nurse
- Part B of Form: Completed by clinician or other clinical officer (if relevant)
- Computer entry and quarterly transmission of data: by IT person (or by other staff working with computer; alternatively, transmit copy manually)

**VAAC and PAC**

- VAAC: supportive supervision of PAC (quarterly)
- PAC: supportive supervision of ART sites (bimonthly for the first six months, then quarterly)

**DI&ADR Center**

- Sending acknowledgment whenever data are received
- Data management, analysis including causality assessment, update reporting (quarterly)

**PV Technical Committee**

- Expert technical advice to DI&ADR

**VAAC, PAC, DI&ADR Center, PV Technical Committee, DAV, MSA, and Others**

- Participation in appropriate responses based on locally generated data, including safety signals

Figure 3 is a schematic presentation of the interconnected roles and responsibilities of different stakeholders grouped according to the different elements of the active surveillance framework.

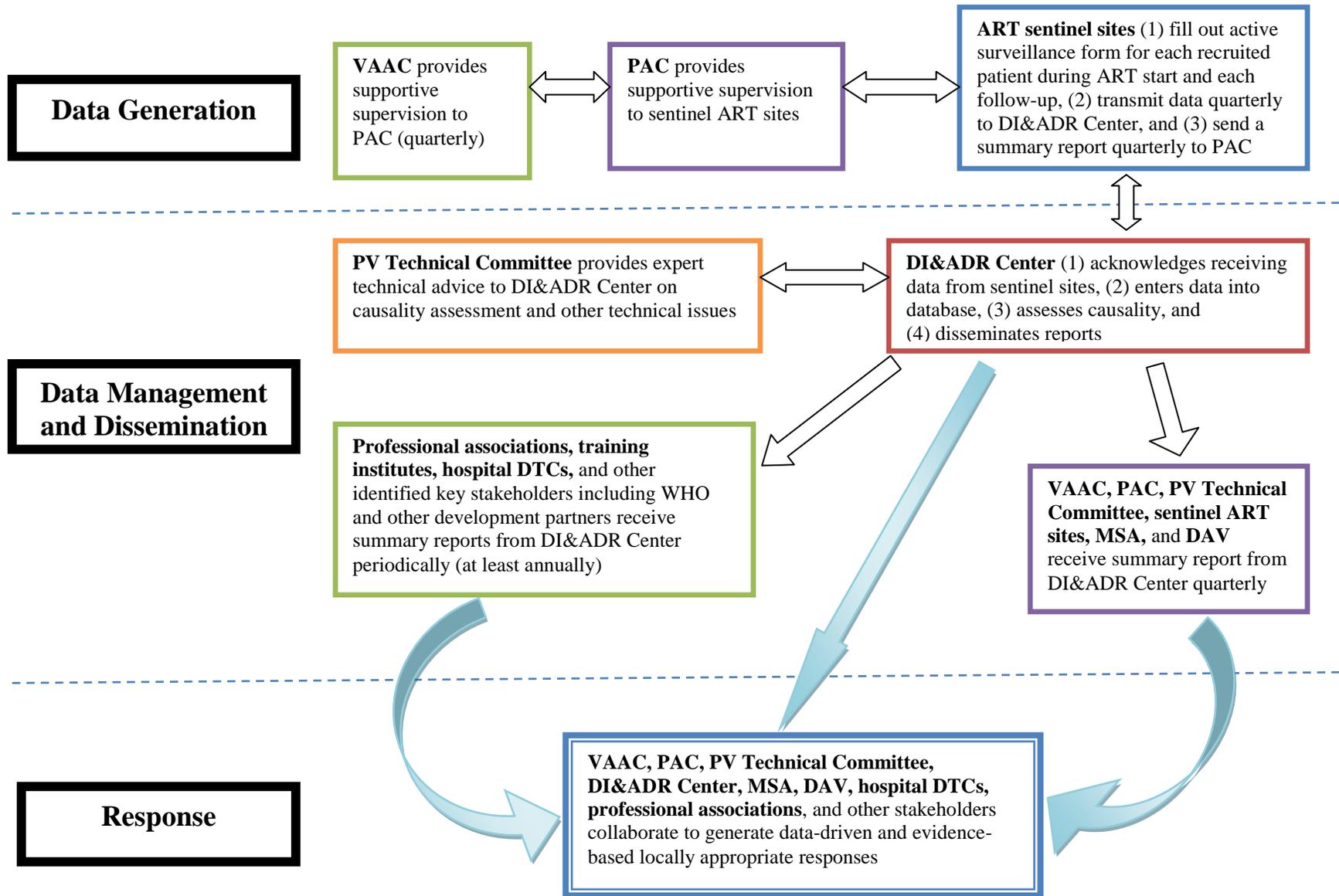


Figure 3. Framework of the Pilot Surveillance Activity, and Roles and Responsibilities of the Stakeholders

## MONITORING AND DISSEMINATION OF THE PILOT ACTIVITY

It is important to monitor the progress of the pilot activity to identify any problems encountered in implementation to allow for refining and adapting implementation strategies, including training. Monitoring the pilot activity provides the basis for documenting lessons learned for subsequent decision making about possible scale-up of active surveillance pharmacovigilance beyond the pilot stage. In most instances, monitoring can be conducted by routine assessment of the Active Surveillance Forms; but in some instances, a need may exist for a limited amount of additional information gathered through selected interviews or assessment of source records. The following areas of focus are proposed for monitoring this pilot activity—

- Number of Active Surveillance Forms received and timeliness of their receipt
- Completeness of Active Surveillance Forms
- Data quality: Validity of data elements contained in the Active Surveillance Forms
- Simplicity and efficiency of the active surveillance activity, for example, time and effort involved in various phases of the activity

Feedback to the sentinel sites on the monitoring of the data collection for completeness and validity must be a regular part of data collection and interpretation. Feedback should be given promptly to sentinel sites in the event of inconsistencies in data collection, missing data, and other related issues that require immediate attention to ensure data quality.

The VAAC and DI&ADR Center will need to develop a plan to effectively communicate the results of the pilot activity to the various stakeholders.

After the pilot ends, the overall experience of its implementation, including results, achievements, and challenges, as well as recommendations for approaches to future scale-up should be disseminated to a wide group of related stakeholders.



## ANNEX 1. DEFINITIONS<sup>16</sup>

### **Active (or proactive) safety surveillance**

Systems whereby active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records.

### **Adverse event**

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

### **Adverse (drug) reaction (ADR)**

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

### **Causality assessment**

The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event. Causality assessment is usually made according to established algorithms.

### **Pharmacovigilance**

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

### **Relationship assessment**

The objective evaluation of the relationship between the administration of a medicine and a health event, taking into consideration duration of therapy to onset of event, response to dechallenge and rechallenge (if performed) and the presence of diseases or other medicines that could have caused the event. This process stops short of attempting to establish a causal relationship but is an essential preliminary.

### **Risk**

The probability of harm being caused; the probability (chance, odds) of an occurrence.

### **Serious adverse event or reaction**

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- is life-threatening;
- is a congenital anomaly/birth defect.

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<sup>16</sup> These definitions are reproduced from the following WHO reference materials:

- WHO. 2009. *A Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines*. Geneva: WHO.
- WHO/the Uppsala Monitoring Centre. 2000. *Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre*. Uppsala, Sweden: the Uppsala Monitoring Centre.

To ensure that there is no confusion or misunderstanding about the difference between the terms “serious” and “severe,” the following note of clarification is provided:

The term “severe” is not synonymous with serious. In the English language, “severe” is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on the outcome of the event on the patient or action criteria serves as the guide for defining regulatory reporting obligations.

**Signal**

“Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.” Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

**Spontaneous report**

An unsolicited communication by health care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

## ANNEX 2. RECOMMENDED RESOURCES NEEDED AND STAFFING PLAN

The pilot is designed to fit into the existing structures and functions of the ART Program and the DI&ADR Center so resources related to new staff or structures are not anticipated. However, the following resources will be required to initiate the pilot:

- **Training** of Sentinel Sites, DI&ADR Center staff, PV Technical Committee staff, and other related stakeholders
- **Simple database** for computer entry of data at ART sites and for data management at the DI&ADR
- **Field-testing, printing, and distributing** the *Pharmacovigilance Active Surveillance Form*
- **Operational:** Internet access, local travel, and IT support

Additionally, for optimal efficiency of the pilot program, it is recommended that a focal person be identified, for example, a coordinator and data manager at the DI&ADR Center, and the primary contact person at each sentinel site. It is also recommended that a team of clinical reviewers representing the PV Technical Committee and other ART hospitals and organizations be identified to technically support the DI&ADR Center in causality assessment and other matters, including decisions on generating locally appropriate responses based on ongoing accumulation of data.



## ANNEX 3. DATA COLLECTION FORM

### VIETNAM ART PROGRAM – SENTINEL SITE ACTIVE SURVEILLANCE FORM FOR ART-NAIVE PATIENTS (PART A)

<b>Patient Unique Identification Number:</b>					
<b>PATIENT STATUS AT START OF ART – COPY FROM RECORDS</b>					
<b>Date of Birth:</b> ____/____/____	<b>Age:</b> ____ yrs	<b>Facility</b> <input type="checkbox"/> _____ <input type="checkbox"/> _____ <input type="checkbox"/> _____	<b>Weight:</b> ____ kgs	<b>WHO Clinical Stage:</b> 1 2 3 4 99 (if missing)	
<b>CONDITIONS</b>	<b>CHECK</b>	<b>MEDICATIONS (CURRENT AND WITHIN PAST MONTH)</b>		<b>LABORATORY TESTS</b>	
Malnutrition				<b>Test</b>	<b>Date</b>
Anemia				Hb (g/dl)	
Alcohol abuse				CD4	
Substance abuse				ALT	
Tuberculosis				Others (specify): Creatinine	
Renal disease					
Liver disease					
Bacterial infection					
Other (specify)					
Other (specify)					



