WHO IMPLEMENTATION TOOL FOR MONITORING THE TOXICITY OF NEW ANTIRETROVIRAL AND ANTIVIRAL MEDICINES IN HIV AND VIRAL HEPATITIS PROGRAMMES

JULY 2018

World Health Organization

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ABBREVIATIONS AND ACRONYMS

ART	antiretroviral therapy
ARV	antiretroviral
aDSM	active tuberculosis drug safety monitoring and management
DAA	direct-acting antivirals
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EDS	Enhanced Data System
EFV	efavirenz
NASCOP	national AIDS and STI control programme
NVP	nevirapine
RAL	raltegravir
TLD	fixed-dose combination of tenofovir disproxil fumarate, lamivudine and dolutegravir
TB	tuberculosis

DEFINITIONS

Active toxicity monitoring. A system in which active measures are taken to detect the presence or absence of adverse drug reactions occurring during or after exposure to a pharmaceutical product. The adverse drug reactions may be detected by interviewing patients, performing specific investigation or by screening patient records.

Active TB drug safety monitoring and management (aDSM). Active and systematic clinical and laboratory assessment of people being treated for drug-resistant tuberculosis (TB) or with new TB medicines or novel multidrug-resistant TB regimens to detect, manage and report suspected or confirmed drug toxicities.

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

Adverse drug reaction. A response that is harmful and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for modifying physiological function. An adverse drug reaction, in contrast to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence: that is, assessed as being at least possibly related to treatment by the reporting or a reviewing health professional.

Pharmacovigilance. The science and activities relating to detecting, assessing, understanding and preventing adverse effects or any other drug-related problem.

Routine toxicity monitoring. Monitoring of treatment-limiting ARV drug toxicity (see below for definition) integrated into the monitoring and evaluation of national HIV treatment programmes using patient monitoring tools and reporting systems.

Signal. Information reported on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or previously incompletely documented. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

Treatment-limiting toxicity. A serious adverse drug reaction that results in drug discontinuation or substitution. This includes serious adverse drug reactions: any adverse reaction that can cause one of the following: death; threatening life; requiring or prolonging hospitalization; disability or permanent damage; or congenital anomaly or birth defect. In addition, any reaction that leads to treatment interruption or requires changing the drug or regimen because of an adverse drug reaction is also considered a serious adverse drug reaction.

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Please send any comments on this tool or suggestions to hiv-aids@who.int

1. INTRODUCTION

1.1 Context

The global scaling up of antiretroviral therapy (ART) under the public health approach of standardized and simplified regimens has registered significant gains, with increasing access to treatment for millions of people and a reduction in the number of people newly infected with HIV and the number of people experiencing HIV-associated morbidity and mortality. By mid-2017, 20.9 million people were receiving ART, and treatment coverage in 2016 reached 53% of the people living with HIV *(1)*.

The 2016 WHO consolidated guidelines on the use of antiretroviral (ARV) drugs *(2)* recommended initiating ART earlier and new first-line alternative treatment options such as dolutegravir (DTG) and efavirenz at the lower dose of 400 mg (EFV 400). The guidelines also recommend darunavir/ritonavir (DRV/r) and raltegravir (RAL) as alternative ARV drugs for second-line treatment. To date, more than 50 low- and middle-income countries have included or plan to include dolutegravir (DTG) as first-line treatment in their national guidelines *(3)*. Moreover, such countries such as Cambodia, China, the United Republic of Tanzania and Zimbabwe have or are considering introducing EFV 400 for use in first-line ART *(4)*.

With the availability of a generic fixed-dose combination of dolutegravir with tenofovir and lamivudine (TLD) and recent pricing agreements that have significantly reduced its cost, more countries are considering transitioning to using DTG for preferred first-line ART. To date, however, data on the safety of DTG and other new ARV drugs are limited in important subpopulations, including young children, pregnant women, people with HIV and TB coinfection and individuals with advanced disease. Among the general population, there are currently limited data from real-world settings on the safety of new ARV drugs, including DTG, within large-scale national treatment programmes. Moreover, central nervous system adverse drug reactions, especially insomnia, have been reported in observational cohorts among individuals receiving DTG *(5,6)*. Reports from cohort studies of a higher risk of immune reconstitution inflammatory syndrome among people receiving integrase inhibitors *(7,8)* have also raised concerns about safety. As a result, early-adopter countries are implementing approaches for monitoring toxicity with the support of partners that are described in later sections of this tool.

In the current context of treatment being rapidly scaled up, prolonged exposure to ARV drugs and transition to new ARV drugs, ARV toxicity clearly needs to be monitored to better understand the risks of ARV drugs under the conditions of actual use. Systematically collecting information about medicines used in a defined population helps to ensure that medicines have an acceptable safety profile and are used appropriately. To address these gaps in safety data, WHO recommended enhanced monitoring and surveillance of toxicity in a recent technical update on transition to new ARV drugs in HIV programmes: clinical and programmatic considerations *(4)*.

This implementation tool builds on the above guidance as well as the WHO 2015 consolidated strategic information guidelines for HIV in the health sector *(9)*, the 2016 consolidated guidelines on the use of ARV drugs for treating and preventing infection *(2)* and the 2017 consolidated guidelines on person-centred HIV patient monitoring and case surveillance *(10)*. It describes in more detail the recommended approaches for routine monitoring of toxicity integrated with the national monitoring and evaluation system and targeted approaches to monitoring toxicity to enable enhanced monitoring and reporting of treatment-limiting toxicity to support country implementation and generation of local data. In addition to recognizing the linkages, coinfected populations and commonalities across TB, hepatitis B and C and with the aim of encouraging integration, this tool also highlights the recommended toxicity monitoring approaches and existing tools across these disease areas. The approaches presented in this tool describe the methods and tools that can be used for monitoring treatment-limiting toxicity associated with new ARV drugs. In this version, the reporting tools provided in the annexes relate to monitoring the toxicity of DTG as a priority since many countries are moving towards adopting it in first-line regimens. Going forward, additional annexes and tools will be developed as countries approve and/or adopt new ARV drugs, and WHO will publish these online.

1.2 Structure and objectives of this tool

This implementation tool aims to support countries in collecting information on treatment-limiting toxicity related to use of new ARV drugs, including DTG, in a structured and systematic way that will enable information to be disseminated and used for decision-making purposes and thereby enhance the quality of care and safety of ARV drug programmes. It does not cover epidemiological surveillance of adverse pregnancy and birth outcomes associated with ARV drugs, since an established approach with an existing protocol and accompanying tools has been developed and is available for country use. Specifically, WHO has established a central registry for the global surveillance of drug safety in pregnancy that includes ARV drugs and should be used for the surveillance of new ARV drugs. Generic model reporting forms, training materials and a data entry programme to help countries in pooling data from in-country pregnancy registries and birth outcome surveillance projects are available for country adaptation *(11)*.

This tool for implementing toxicity monitoring therefore focuses on monitoring approaches within the context of national treatment programmes, which includes pregnant women but does not include surveillance of congenital abnormalities, which is covered by the surveillance of drug safety in pregnancy mentioned above. In this tool, two approaches to monitoring toxicity are recommended to support the introduction of new ARV drugs into HIV and viral hepatitis programmes. As a result, this tool is divided into the following two sections to reflect this. Part 1 focuses on routine toxicity monitoring integrated within the national monitoring and evaluation system and implemented at all ART sites. Part 2 covers active toxicity monitoring implemented at select sites to complement routine toxicity monitoring and enable more detailed information on treatment-limiting toxicity related to specific new ARV drugs, adverse drug reaction management and outcomes to be captured. In addition, guidance and available resources and tools for the active and routine toxicity monitoring of drugs used within TB and hepatitis B and C are also provided to support countries in implementing and adapting approaches across these diseases and, where feasible, to promote the integration of data collection and reporting systems.

In short, this implementation tool aims to support countries in:

- improving the safety knowledge of new ARV drugs by providing tools (for DTG) and guidance to support the identification and establish the prevalence and severity of known treatment-limiting toxicity;
- enabling the monitoring of how toxicity related to new ARV drugs affects adherence and treatment outcomes, including treatment discontinuation, disability or incapacity, inpatient hospitalization or prolonged existing hospitalization, life-threatening illness and death;
- determining how comorbidities as well as concomitant medicines (especially those with overlapping toxicity profiles), including traditional medicines and dietary supplements, effect the incidence, nature and/or severity of toxicity related to new ARV drugs; and
- identifying rare or unexpected types of toxicity associated with the long-term use of new ARV drugs that have not previously been identified.

1.3 Target audience

This tool is primarily intended for national and subnational ART programme managers and other personnel involved in designing and using monitoring and evaluation systems, pharmacovigilance, toxicity monitoring, surveillance and tools for collecting, analysing and using HIV health sector and viral hepatitis data. This tool may also be of interest to technical partners and other key stakeholders involved in supporting the design and implementation of HIV health sector and hepatitis monitoring and evaluation systems with a focus on toxicity and patient monitoring.

1.4 Toxicity monitoring approaches and guidance for HIV, TV and hepatitis B and C

The introduction of new drugs within HIV, TB and hepatitis C programmes and the long-term (lifelong) use of existing antiviral drugs for treating hepatitis B have created a clear need to implement toxicity monitoring of drugs across these disease areas. The significant overlap in the burden of these diseases and commonalities across programmes present opportunities for integrating toxicity monitoring activities, especially for coinfected individuals. As new drugs are introduced, existing toxicity monitoring approaches and data collection activities used in these disease areas, either as part of routine patient monitoring or more enhanced active monitoring activities, should be reviewed and opportunities explored for use by adapting tools and existing reporting systems and infrastructure. At the same time, specific programme needs and key differences across diseases may necessitate different approaches or adaptation of tools in certain subpopulations. Table 1 presents some of the key elements in toxicity monitoring approaches, guidance and available tools and resources for HIV, TB and hepatitis B and C with the aim of supporting country adaptation and use.

Table 1. Toxicity monitoring approaches and guidance for HIV, TB and hepatitis B and C

	HIV	TB	HBV	HCV
Treatment duration	**Life long**	**Varies [6-20 months]** *(12)*	**Lifelong**	**3 months [varies 2-6 months]**
Specific programme requirements and needs	Safety data lacking for DTG for pregnant women, children and people coinfected with TB and HIV	WHO issued an interim policy on the use of two new drugs, bedaquiline and delamanid, in 2013 and 2014, respectively, and recommended a shorter course multidrug-resistant TB regimen for selected people with TB in 2016; active TB drug safety monitoring and management (aDSM) is one of the conditions set for implementing these policies	Monitoring both treatment-limiting toxicity and long-term adverse drug reactions	Monitoring treatment-limited toxicity related to newly introduced direct-acting antiviral drugs
Major toxicity concerns	Hypersensitivity reactions, electrocardiographic abnormalities, clinical jaundice, renal toxicities, anaemia, lipodystrophy, lactic acidosis or severe hepatomegaly, hepatotoxicity, hypersensitivity reactions, severe skin and hypersensitivity reactions, CNS toxicity, diarrhoea, decreases in bone mineral density *(2)*	Nausea and vomiting, diarrhoea, arthralgia, dizziness and vertigo, hearing disturbances, headache, sleep disturbances, electrolyte disturbances, abdominal pain, anorexia, gastritis, peripheral neuropathy, depression, tinnitus, allergic reaction, rash, visual disturbances, seizures, hypothyroidism, psychosis, suicidal ideation, hepatotoxicity, renal failure and electrocardiographic abnormalities *(13)*	**Tenofovir:** renal toxicity, including tubular dysfunction; small decreases in bone mineral density with osteopaenia or osteoporosis during the early phases of treatment have also been reported **Entecavir:** proximal tubular dysfunction is less common than with tenofovir	Direct-acting antiviral drugs are well tolerated, with minor adverse drug reactions; the most common reported adverse events of direct-acting antiviral drugs are fatigue, headache, insomnia and nausea Direct-acting antiviral drugs are not recommended during pregnancy
Recommended toxicity monitoring approaches	**Routine** toxicity monitoring of all ARV drugs in use via the patient monitoring system complemented by **Active** toxicity monitoring to support the safe introduction of specific new ARV drugs	**Active** TB drug safety monitoring and management for individuals receiving multidrug-resistant TB treatment	**Routine** toxicity monitoring via the patient monitoring system	**Routine** toxicity monitoring via the patient monitoring system Countries can also consider implementing active toxicity monitoring for new direct-acting antiviral drugs to complement routine toxicity monitoring activities
Available tools and resources for toxicity monitoring	1) WHO 2017 patient monitoring tools and guidance *(10)* 2) Technical update on transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations *(4)* 3) WHO Implementation Tool for Monitoring the Toxicity of New Antiretroviral and Antiviral Medicines in HIV and Viral Hepatitis Programmes (www.who.int/hiv/topics/arv_toxicity/en) 4) WHO training slides for monitoring the toxicity of new ARV drugs in HIV and viral hepatitis programmes (www.who.int/hiv/topics/arv_toxicity/en) 5) WHO central repository for toxicity-related data on DTG (www.who.int/hiv/topics/arv_toxicity/en)	1) aDMS framework for implementation *(14)* 2) aDSM training package *(13)* 3) WHO GTB-TDR Global aDSM Database (www.who.int/tdr/research/tb_hiv/adsm/en)	Generic hepatitis patient monitoring card that captures toxicity and adverse drug reactions related to hepatitis B drugs (Annex 4)	Generic hepatitis patient monitoring card that captures toxicity and adverse drug reactions related to hepatitis C drugs (Annex 4)

2. PART 1: ROUTINE MONITORING OF THE TOXICITY OF NEW ARV DRUGS

2.1 Background

Monitoring the toxicity of ARV drugs is a critical component of patient monitoring systems. Knowledge of the management of adverse drug reactions associated with the use of new ARV drugs and risk factors such as other illnesses and conditions and drug interactions with other medications will generate much-needed safety data to help to improve care and treatment outcomes. WHO recommends that countries use a standardized approach to integrate toxicity monitoring within national monitoring and evaluation systems *(9,15)*. This applies to all ARV drugs used in treatment programmes, including newly introduced drugs such as DTG.

Routine toxicity monitoring provides data on the prevalence and clinical significance of serious toxicity. The 2013 and 2016 WHO guidelines on consolidated ARV treatment *(2)* recommend a symptom-directed approach to laboratory monitoring of the safety and toxicity of ART regimens. The 2017 consolidated guidelines on person-centred monitoring and case surveillance *(10)* further build on this guidance, defining the key toxicity prevalence indicator to be collected (Table 2) and providing patient monitoring tools to capture treatment-limiting toxicity as part of routine reporting (Box 1).

This section describes these tools and defines the toxicity prevalence indicator recommended for ARV drug toxicity monitoring in the 2017 patient monitoring guidelines *(10)*. This indicator is not intended to be comprehensive or enable monitoring of all key issues related to ARV drug toxicity nor is it designed to assess whether the objectives of this monitoring tool have been met. Rather the proposed approach defines a minimum set of data elements for reporting on the magnitude of toxicity and how it affects treatment discontinuation *(16)*.

Table 2. National ARV drug toxicity indicator

Indicator	Programme relevance and interpretation
Toxicity prevalence: percentage of people receiving ART with treatment-limiting toxicity	Measures how toxicity affects treatment outcomes. Helps to guide national policy on ART regimens, diagnosis, strategies for preventing toxicity, health-care worker training and retention in care

Source: Consolidated strategic information guidelines for HIV in the health sector (9).

Box 1. Factors to support the implementation of routine toxicity monitoring of new ARV drugs

Routine toxicity monitoring of new ARV drugs can be supported by strengthening the national patient monitoring system, introducing and ensuring that the new indicator on the proportion of people receiving ART with treatment-limiting toxicity is integrated into the monitoring and evaluation system, introducing electronic medical records to support reporting, updating standard data collection tools, including the HIV card and ART registers for children and adults, and ensuring that new codes for major types of toxicity and treatment substitution or interruption are captured in patient monitoring tools and used.

Special considerations for children[1]

Data on ARV drug toxicity among children are limited. Children face lifelong treatment and are exposed to ARV drugs for an ever-increasing length of time throughout postnatal growth and development. Cumulative toxicity may only become apparent after long periods of exposure. Routine monitoring of ARV toxicity among children is therefore critical. For hepatitis C the newly released treatment guidelines recommend deferral of treatment until the age of 12 years[2]. The reporting tools and indicators described in this section should also be used to monitor and report on ARV drug toxicity among children as part of the routine monitoring and evaluation system.

2.2 Standardized data collection and reporting tools for routine toxicity monitoring

HIV care and treatment card

The HIV care and treatment card is designed to be completed for all individuals entering care at a facility and serves as the primary data source for patient monitoring. The card contains the HIV-specific minimum data set and links to other services the individual may be receiving. Fig. 1 highlights the data elements and codes related to ARV toxicity to be used to complete the HIV card. The front page of the card captures the reasons for ARV drug substitutions and treatment interruption, including toxicity, and the encounter page enables reporting of treatment-limiting toxicity and adverse drug reactions at each visit using standardized toxicity codes and the reasons for non-adherence, which also includes toxicity and side-effects. Toxicity is captured under three sections in the HIV card: (1) substitution within first-, second-or third-line treatment (front page); (2) ART interruptions (front page); and (3) reasons for missed doses (encounter page). Countries should ensure that national adaptations and versions of the HIV card and ART register contain the elements and reporting elements described below to allow routine reporting of treatment-limiting ARV toxicity.

Box 2. What is new on the HIV patient card for monitoring the toxicity of ARV drugs

- "Potential side-effects" updated to "Treatment-limiting toxicity or adverse effects".
- Code 1 included for toxicity as a reason (among others) for substitution and discontinuation of ARV drugs and code 1 for poor adherence due to toxicity.
- The list of major types of toxicity was revised and accompanied with individual coding to capture major types of ARV drug toxicity as defined in the 2016 WHO ARV drug guidelines *(2)* (Fig. 1).

1. Children and infants are defined as follows: a child is 1–9 years old. An infant is a child younger than one year old.
2. Consolidated guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection. Geneva: World Health Organization; 2018.

Figure 1. HIV care and treatment patient card

HIV care and treatment patient card: front page

Status at enrolment: Symptomatic disease: ☐Y ☐N	**Transfer in:** ☐On ART ☐Tx faillure/interruption ☐Naive		
Unique no.: ☐☐☐☐☐☐☐☐	Health district:	Health unit:	Health clinician/ team:
Name:	PT clinic no.:	DOB:	Age:
Sex: ☐M ☐F	Marrial status:		
Address:	District:	Telephone (whose):	
Treatment supporter/med pick-up if ill? ☐Y ☐N	If yes, who:		
Address:		Telephone (whose):	
Home-based care provided by:			

Family Status			
Relation to patient	HIV P/N	Unique no.	Date of Death
			__/__/____
			__/__/____
			__/__/____
			__/__/____
			__/__/____

HIV-exposed infant follow up						
Exposed infant (Named/ no.)	DOB	Infant-feeding practice at 3 mos.	CTX started by 2 mos	HIV test Type/ Result	Final Status	(if confirm +) Unique ID

Date	HIV care			
__/__/____	First HIV+ test			
__/__/____	Confirmed HIV+ test	HIV ☐1 ☐2	Ab/virological test	Where:
__/__/____	Enrolled in HIV care (HIV patient card open)	☐HIV care transfer in from:		

Drug allergies & interactions	Relevant chronic conditions	Concomitant medications

TB status	TB reg#		
TB patient therapy start date: __/__/___	TB symptom+ date: __/__/____	Test type (circle)	result: S C X	TB Rx start date: __/__/____
TB prev. therapy stop date: __/__/___	Date of investigation: __/__/___	☐TB + ☐MDR-TB		TB Rx stop date: __/__/___

Figure 1. HIV care and treatment patient card

HIV care and treatment patient card: front page (cont.)

Prior ARVs				
Y (✔)	Prior ARV	Date		
	None			
	ARVs during pregnancy or breastfeeding	__/__/____	Where:	ARVs:
	ARV prophylaxis for HIV-exposed infant	__/__/____	Where:	ARVs:
	Earlier ARV not transfer in	__/__/____	Where:	ARVs:
	ARVs for PEP or PrEP	__/__/____	Where:	ARVs:

ART					
			COHORT (month/ year): __/____		
__/__/____	Art transfer in from		ARVs:	Last VL:	
__/__/____	Start ART 1st-line initial regimen				
At start ART:	CI. Stage:	CD4:	☐TB+	☐TB Rx	☐TB-exposed infant
	☐HBsAg+	☐HCV RNA+	☐Pregnant	☐Postpartum	☐Breastfeeding
Susbtitute within 1st-line					
__/__/____	New regimen		Why:		
__/__/____	New regimen		Why:		
Switch to 2nd-line (or substitute within 2nd-line)					
__/__/____	New regimen		Why:		
__/__/____	New regimen		Why:		
Switch to 3rd-line (or substitute within 3rd-line)(added)					
__/__/____	New regimen		Why:		
__/__/____	New regimen		Why:		

Reasons for ARV drug substitution in 1/2/3rd line ART are reported here. Codes for substitutions as follows:

1. Toxicity/side effects
2. Pregnancy
3. Due to new TB
4. New drug available
5. Drug out of stock
6. Other reason (specify)

ART treatment interruptions - STOP or missed drug pick-up						
Date	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____
Why						
Date if restart	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____

Reasons for stopping treatment are reported here. Stop codes are as follows:

1. Toxicity/side effects
2. Serve illness, hospitalization
3. Drugs out of stock
4. Patient lacks money
5. Excluded HIV infection in infant
6. Other

Follow-up status	Date					
Lost to follow up	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____
Transfer out	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____	__/__/____
-- to where						
Dead	__/__/____					

Figure 1. HIV care and treatment patient card

HIV care and treatment patient card: encounter page

Unique no. ☐☐☐☐☐☐☐☐ HIV PATIENT CARD Name:

Date | Check if sheduled. | Write in alternate pick-up if ill.	Follow-up date	Duration in months since first starting ART & since starting current regime	Wt/ Ht | Ht at fisrt visit if adult | If child record Wt/ Ht, +/- oedema	Pregnancy/ RH-FP choices | If child record | MUAC | Write age in mos. if ≤59 mos | Vaccination	TB status (see codes)	Hepatitis information	Treatment limiting toxicities | adverse reactions	Comorbidities and coinfections (including new OIs, STIs and major NDCs) If child, include nutritional problems	
				BASELINE					
☐									
☐									
☐									
☐									
☐									

Treatment-limiting toxicity to be reported here using the following codes in bold:

- **GI** (gastrointestinal: nausea, diarrhoea, abdominal pain, vomiting)
- **P**eripheral neuropathy (burning, numbness or tingling)
- **CNS** (central nervous system: dizzy, anxiety, nightmare, depression, seizures)
- **Hep**atic dysfunction (jaundice)
- **Haem**atological (anaemia, neutropaenia)
- **F**atigue
- **H**eadache
- **B**one dysfunction (fractures, osteopenia)
- **M**etabolic (body fat changes, hyperglycaemia, dyslipidaemia)
- **K**idney dysfunction (nephrolithiasis, renal insufficiency)

Figure 1. HIV care and treatment patient card

HIV care and treatment patient card: encounter page (cont.)

	Co-trimoxazole | Adhere? Dose/ days	TB preventive therapy | Record start or complete (date)	Other meds dispensed (including TB/ MDR-TB, traditional medicine, nutritional supplements, opioid substituion therapy)	ART		Investigations (record when test requested and results received in relevant visit date rows)			Refer or link/ provide (including nutritional support and infant feeding (use follow-up education page notes)) If hospitalized, no. of days
				No. missed doses/ Why	Regiment/ Dose/ No. days dispensed	CD4 if <5 years, record CD4%	Viral load	Hgb, RPR/ TPHA, HBsAg, HCV Ab/ RNA, sputum/ CXR/ Xpert, infant Ab/ HIV virological test, other	
BASELINE									

Reasons for non-adherence (any missed dose (s)) should be reported here using the following codes:

1. Toxicity or side-effect
2. Forgot
3. Asleep
4. Busy
5. Change of routine
6. Travel cost
7. Distance to clinic
8. Patient lost or ran out of pills
9. Stock-out
10. Too ill
11. Pill burden
12. Felt well
13. Depression
14. Alcohol or substance abuse
15. Stigma or disclosure concerns
16. Lack of food
17. Poor adherence
18. Other (specify)

Figure 2. ARV toxicity data elements to be completed

ART register: The ART register contains a subset of key information from the HIV patient card, including treatment-limiting toxicity. This should be completed for all ARV drugs, including DTG.

District:	Health facility:	Cohort year:	Month:

	Registration and personal information						Status at ART start			Pregnancy (also record "P" as follow-up status)					1st-line regimen	2nd-line regimen	3rd-line regimen
	ART start date	Unique ID no.	Patient clinic ID	Name | Surname | Given Name	Sex	Age	Pregnant Breastfeeding	TB+	CD4 (% if U5)	Preg 1	Preg 2	Preg 3	Preg 4	Original regimen	Substituitions 1st Reason/ Date 2nd reason/ Date	Switches/ Substituitions 1st Reason/ Date 2nd reason/ Date	Switches/ Substituitions 1st Reason/ Date 2nd reason/ Date
1																	
2																	
3																	
4																	
5																	

Sub-totals								
Adult/ adolescent 1st-line regimens	Child <10 years 1st-line regimens	Adult/ adolescent 2nd-line regimens	Child <10 years 2nd-line regimens	Adult/ adolescent 3rd-line regimens	Child <10 years 3rd-line regimens	Reasons for substituion	Reasons for switch to 2nd- or 3rd-line regimens	Treatment-limiting toxity
1a = TDF-3TC-EFV 1b = TDF-FTC-EFV 1c = ... 1d = Other	4a = ABC-3TC-EFV 4b = ABC-3TC-LPV/r 4c = AZC-3TC-LPV/r 4d = ... 4e = Other	2a = TDF-3TC-ATV/r 2b = TDF-FTC-ATV/r 2c = TDF-3TC-LPV/r 2d = TDF-FTC-LPV/r 2e = AZT-3TC-ATV/r 2f = AZT-3TC-LPV/r 2g = ... 2h = Other	5a = AZT-3TC-RAL 5b = ABC-3TC-RAL 5c = AZT-3TC-EFV 5d = AZT-3TC-RAL 5e = TDF-3TC-EFV 5f = TDF-3TC-RAL 5g = ... 5h = Other	3a = DRV/r-DTG-??? 3b = DRV/r-RAL-??? 3c = DTG-??? 3d = RAL-??? 3e = DVR/r-??? 3f = ... 3g = Other	6a = DRV/r-??? 6b = DRV/r-DTG 6c = DRV/r-RAL 6d = ... 6e = Other	1. Toxicity/ side-effects (record code for toxicity) 2. Pregnancy 3. Due to new TB 4. New drug available 5. Drug out of stock 6. Other reason (specify)	7. Clinical treatment failure 8. Immunological failure 9. Virological failure	1. GI 2. Skin 3. CNS 4. Hepatic dysfunction/ jaundice 5. Haematological 6. Fatigue 7. Bone dysfunction 8. Metabolic 9. Headache 10. Kidney dysfunction

ARV toxicity data elements to be completed

- Enter the above codes highlighted in red for reasons for substitution in the columns highlighted blue using the code **1 for toxicity.**
- Record the corresponding code for treatment-limiting toxicity (codes highlighted in green) beside it; for example, for gastrointestinal adverse drug reactions, code 1 would be recorded.

Instructions for key indicators of ARV drug toxicity prevalence

The key indicator for monitoring ARV drug toxicity included in the minimum data set for HIV patient monitoring according to the 2017 WHO consolidated guidelines on person-centred HIV patient monitoring *(10)* is treatment-limiting toxicity (see Fig. 3 and the definitions section for further details). Table 3 describes the indicator and provides instructions for calculation. It is recommended that this indicator be captured via electronic systems using electronic medical records.

Table 3. Instructions for indicators of ARV drug toxicity prevalence

Indicator code and name	ART.12 Toxicity prevalence
Indicator definition	Percentage of people receiving ART with treatment-limiting toxicity
Overview	This indicator measures the impact of toxicity on treatment outcomes. ARV drug–associated toxicity is among the most common reasons reported for poor adherence to ART, treatment discontinuation or substitution of drugs. Routine monitoring will provide data on prevalence and clinical significance of serious types of toxicity and how they affect patient outcomes and attrition. It is a new indicator designated for national programme monitoring in the 2015 WHO consolidated strategic information guidelines for HIV in the health sector *(9)*
Priority level	National, subnational, facility
Numerator	Definition: number of people living with HIV and receiving ART within the past 12 months who substituted a regimen or interrupted or discontinued treatment because of toxicity Data sources: HIV patient card, ART register Data elements: ART start date, ART follow-up status, ARV drug regimen, date substituted (within first-, second- or third-line regimen), reason substituted, toxicity or serious drug reaction, number of missed ART doses, reason for poor ART adherence
Denominator	Definition: ART.3. Numerator: number of people living with HIV who are currently receiving ART [at the end of the reporting period] Data source: ART register Data elements: ART follow-up status
Data collection method	Denominator: this is the numerator for ART.3 ART coverage *(10)* Numerator: for everyone identified in the denominator, in the ART register, look at the last columns on the first page labelled "substitutions" within first-, second- and third-line regimens. Count people if they have substituted within any regimen during the reporting period (see date) and the reason is "toxicity or serious drug reactions" (code = 1). Similarly, go through the relevant follow-up months of the ART register (note: month columns will differ for every cohort; for example, it could be months 0–11 for an ART cohort starting in January 2015 or months 11–22 for an ART cohort starting in January 2014) and count everyone with treatment interruption (no ARV drug regimen code recorded). For these people, pull out their HIV patient cards and find the reason for their poor adherence (number of missed ART doses/why column). Count those with the reason "toxicity or side-effects" (code = 1) recorded.
Frequency	This indicator is best tallied at the end of the year when tallying ART.3 ART coverage
Disaggregation	For each person, note the sex, age and current TB treatment on page 1 of the ART register. Also note the ARV drug regimen (code) the person was receiving when experiencing the toxicity-related drug substitution and the associated toxicity category or categories recorded. • Sex • Age (younger than 15 years old or 15 years and older) • TB and HIV coinfection • ARV drug regimen • Toxicity categories from the minimum dataset

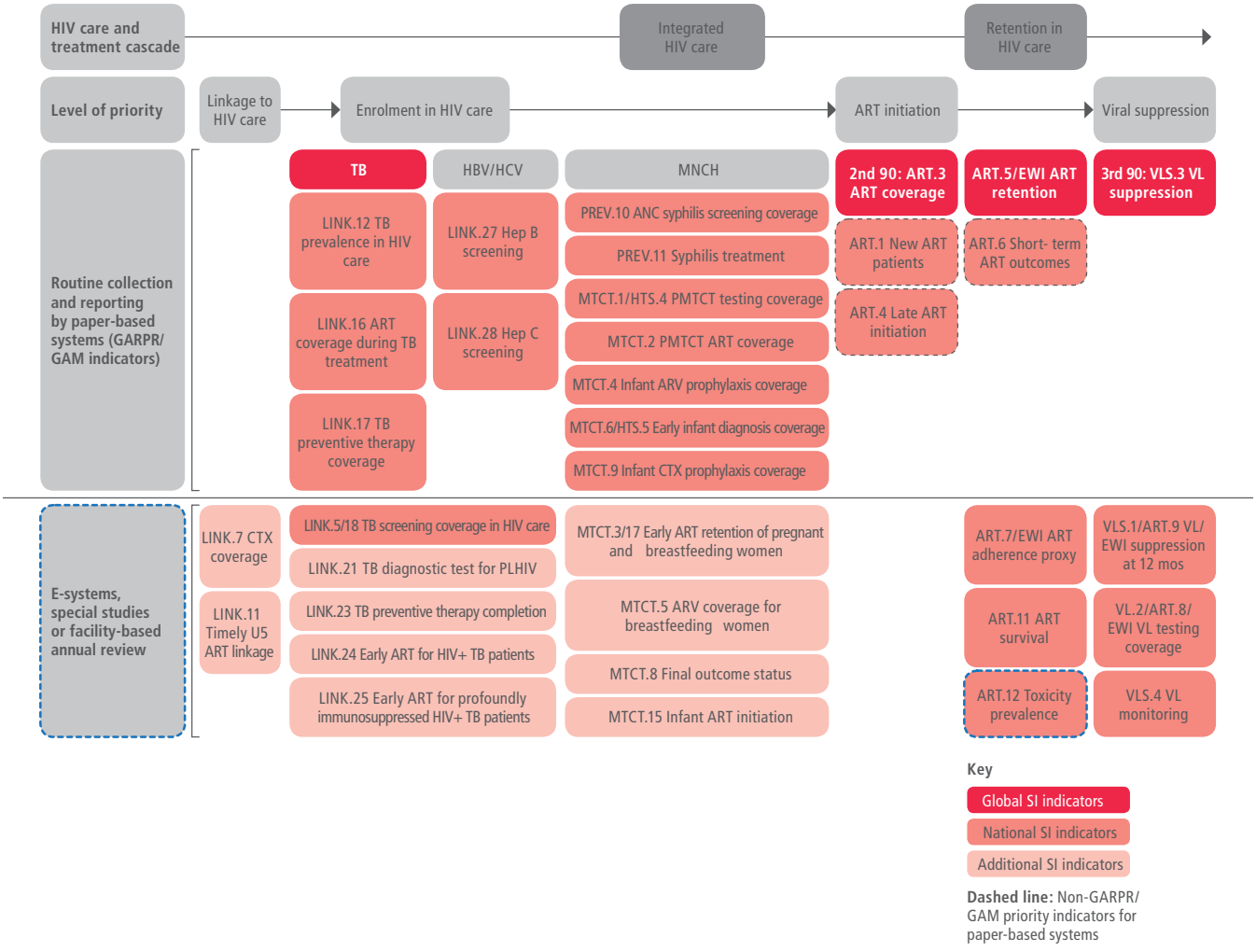
Source: Consolidated strategic information guidelines for HIV in the health sector *(9)*.

When there is a signal alert, further investigation and analysis can be conducted at the facility level, including analysing the outcomes of adverse drug reactions, to support follow-up and remedial action and supplement the information provided by the indicator above.

Box 3. What is new?

- Revised denominator definition to include all those "currently on ART" instead of "on ART in the past 12 months" to align with ART.3 ART coverage numerator.
- A definition of treatment-limiting toxicity has been added to the minimum dataset and adapted into the generic HIV patient card.

Figure 3. Overview of the global, national and additional indicators from the HIV patient monitoring system



Source: Consolidated guidelines on person-centred HIV patient monitoring and case surveillance *(10)*.

2.3 Routine toxicity monitoring for hepatitis B and C

The approach of routinely monitoring toxicity via the patient monitoring system and tools described in this section is also relevant and applicable for monitoring treatment-limiting toxicity associated with the WHO-recommended antiviral drugs for the treatment of hepatitis B infection (tenofovir and entecavir) and hepatitis C infection (direct-acting antiviral drugs). Tenofivir is also used to treat hepatitis B and HIV co-infected individuals.

In general, people with hepatitis C infection tolerate the newly licensed direct-acting antiviral drugs well, with treatment limited to 12 weeks (although this can vary from 8 to 24 weeks based on cirrhosis status and the type of direct-acting antiviral drugs used) and only minor side effects reported. The most common adverse events associated with direct-acting antiviral drugs include, fatigue, headache, insomnia and nausea. A recent systematic review conducted to inform the 2018 WHO hepatitis C treatment guidelines currently being developed found that treatment discontinuation because of adverse events was very infrequent: <1% in people with hepatitis C without and with cirrhosis in the following pan-genotypic regimens: sofosbuvir + velpatasvir, glecaprevir + pibrentasvir and sofosbuvir + daclatasvir *(17)*.

For hepatitis B treatment, renal toxicity has been reported, including proximal tubular dysfunction and some decreases in bone mineral density during the early phases of treatment with tenofovir. Tubular dysfunction is less common with entecavir than tenofovir *(18)*.

Given the above and given the importance of generating safety data to inform national hepatitis programmes as new drugs are introduced, similar to HIV, routine monitoring using patient monitoring cards is recommended. WHO has developed a template for a chronic hepatitis B and C patient management card that captures and enables reporting of treatment-limiting toxicity in a standardized manner (see Annex 4). Countries can adapt this to country needs.

3. PART 2: ACTIVE MONITORING OF THE TOXICITY OF NEW ARV DRUGS

3.1 Background

The 2015 WHO consolidated strategic information guidelines for HIV in the health sector *(9)* and the 2017 WHO technical update on transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations *(4)* recommend, in addition to routine toxicity monitoring (as outlined in the previous section), that countries implement active approaches to monitoring toxicity to address the needs of ART and prevention programmes while transitioning to new ARV drugs. Box 4 summarizes these approaches.

Box 4. WHO-recommended approaches to monitoring ARV drug toxicity

1. Actively monitoring drug toxicity (the focus of this section)
2. Surveillance of ARV drug toxicity during pregnancy through the ARV drug pregnancy registry and surveillance of congenital abnormalities (covered by the surveillance of drug safety in pregnancy) *(19)*
3. Actively monitoring ARV drug toxicity in mother–infant pairs during breastfeeding (up to 24 months)[3]

Source: Consolidated guidelines on person-centred HIV patient monitoring and case surveillance *(10)*.

For active monitoring of ARV drug toxicity, WHO *(4)* recommends "using this approach to monitor emerging toxicity issues and/or new ARV drugs that require strengthened monitoring of potential central nervous system and serious immune reconstitution inflammatory syndrome reactions associated with DTG." Active toxicity monitoring should be linked and, where feasible, use existing pharmacovigilance systems in countries to complement and augment reporting and promote the safe use of new ARV drugs. Integrating activities and data generated by drug regulatory authorities and HIV treatment programmes under the health ministry is essential and can be promoted by using unique identifiers and ensuring that the systems are interoperable under use.

Actively monitoring the toxicity of new ARV drugs is intended to complement the routine toxicity monitoring, providing an inexpensive but robust approach that is added onto routine patient monitoring to capture both known and unknown types of treatment-limiting toxicity (Table 4). It enables specific monitoring of the adverse drug reactions associated with specific ARV drugs as well as other factors such as drug–drug interactions and comorbidities. It also provides an additional active approach to reporting and quantifying the frequency and severity of expected and unanticipated adverse drug reactions among people receiving lifelong treatment with new ARV drugs. Moreover, this approach seeks to address such challenges as underreporting caused by overburdened health-care systems and health-care workers, resource constraints and limited laboratory capacity to identify adverse drug reactions while maintaining simplicity of use, low cost and linkage to existing monitoring and evaluation systems.

3. This can be captured by the pregnancy registry, or specific studies or cohorts can be established to follow up breastfeeding women and their infants.

Table 4. Additional data and specificity captured by active toxicity monitoring

Data element	Routine toxicity monitoring	Active toxicity monitoring
Management of adverse drug reactions	Partly (drug substitutions resulting from toxicity captured)	✔
Seriousness of adverse drug reactions	✖	✔
Outcome of adverse drug reactions (resolved, requires or prolongs hospitalization, disability, death etc.)	✖	✔

Existing country approaches to active toxicity monitoring of new ARV drugs

Several early-adopter countries that have introduced DTG into their first-line ART regimens either in pilot projects (such as Nigeria and Uganda) or nationwide rollout (Botswana, Brazil and Kenya) have implemented or are currently developing active toxicity monitoring approaches. Table 5 summarizes the key features of these approaches.

Table 5. Summary of DTG active toxicity monitoring in early-adopter countries

Country	Key partners and implementers	Number of people initiating DTG	Active toxicity monitoring	Key characteristics and challenges
Brazil	Department of STI/AIDS and Viral Hepatitis and Brazilian Heath Regulatory Agency (ANVISA) – Ministry of Health	73 000 initiating DTG as of November 2017 (first and third line)	✔	• Questionnaire completed by pharmacy personnel collecting information on the type and duration of any suspected adverse drug reaction, severity of reaction, clinical status before onset of the adverse drug reaction, comorbidities and use of other drugs at drug dispensation (Annex 2). • Data captured by questionnaire entered online into the database of the national logistic control system of medicine and linked to patient records. • Training provided to personnel in administering the questionnaire. • Pilot implemented in 10 sentinel sites in five regions selected based on the number of new ART initiators in the past 12 months and regional representation between April and June 2017. • Active DTG toxicity monitoring extended to all ART sites as of July 2017.
Kenya	Ministry of Health, ICAP at Columbia University, Clinton Health Access Initiative		✔	Active toxicity monitoring for DTG is being implemented as follows. • Health-care worker training and sensitization materials developed on ARV drug optimization include pharmacovigilance for ARV drugs. • New monitoring and evaluation indicators to track new ARV introduction include indicators on adverse drug reactions. • Twenty-four sites identified for piloting an enhanced data system with active toxicity monitoring using an adverse drug reaction clinical screening and assessment tool. • A site assessment tool that includes questions about facility-level reporting of adverse drug reactions to the Pharmacy and Poisons Board will provide an understanding of how the existing national pharmacovigilance system is being used and how it may be strengthened.

Table 5. Summary of DTG active toxicity monitoring in early-adopter countries

Country	Key partners and implementers	Number of people initiating DTG	Active toxicity monitoring	Key characteristics and challenges
Nigeria	Ministry of Health, Clinton Health Access Initiative			Two forms of toxicity monitoring are in place. **Active monitoring** • Operational research with enhanced toxicity monitoring among a selected cohort is currently underway to gather data to assist later national scale-up. • Patients are assessed for adverse drug reactions at months 2, 10 and 16 after initiating DTG. • Health records are reviewed for laboratory abnormalities, including viral load, CD4, regimen switches, adverse drug reactions, opportunistic infections, retention and adherence. • Health-care providers are also interviewed at months 2, 10 and 16 on their perceptions of tolerability. • Special emphasis is placed on recognizing neuropsychiatric adverse drug reactions and immune reconstitution inflammatory syndrome. • Women who become pregnant will be switched to alternative therapy but monitored up until delivery for adverse pregnancy outcomes. **Pharmacovigilance** • National system for monitoring drug-related adverse drug reactions. • Reports filed by clinical staff for all grade 3 or 4 adverse reactions,[3] compiled by facility pharmacists, who forward them to the state drug regulatory office. State offices then forward them to the national regulatory agency, which is responsible for analysis and providing feedback as necessary.
Uganda	Ministry of Health, Clinton Health Access Initiative			Two forms of toxicity monitoring are in place. **Active monitoring** • Operational research with enhanced monitoring among a selected cohort is currently underway to gather data to assist later national scale-up. • New initiators of ART and people receiving ART but experiencing side-effects are assessed for adverse drug reactions at months 1 and 6 after initiating DTG. • Health records are reviewed for laboratory abnormalities, including viral load, opportunistic infections, regimen switches, adverse reaction, retention and adherence. • Health-care providers are also interviewed at months 1 and 6 on their perceptions of tolerability. • Special emphasis is placed on recognizing neuropsychiatric adverse drug reactions and immune reconstitution inflammatory syndrome. • Women who become pregnant will be switched to alternative therapy but monitored up until delivery for adverse pregnancy outcomes. **Pharmacovigilance** • National system for monitoring drug-related adverse drug reactions. • Reports filed by clinical staff for all grade 3 or 4 adverse drug reactions, using an online system with hard copies submitted to regional coordinating centres. • Central data analysis is conducted and reported to WHO, National Drug Authority, industry and other interested bodies. • An annual report is compiled and filed on the National Drug Authority website.

3. Grade 3 adverse drug reaction defined as severe but not life threatening; hospitalization required; limitation of the patient's ability to care for himself or herself. Grade 4 adverse drug reaction defined as life threatening; urgent intervention required.

Table 5. Summary of DTG active toxicity monitoring in early-adopter countries

Country	Key partners and implementers	Number of people initiating DTG	Active toxicity monitoring	Key characteristics and challenges
Botswana	Ministry of Health; Botswana-Harvard Partnership; University of Pennsylvania; Botswana–University of Maryland School of Medicine Health	40 000	✖	Active toxicity monitoring for DTG initiators has not yet been implemented, but the following activities have been implemented to monitor the adverse effects of DTG using other approaches: • **Surveillance of congenital abnormities and pregnancy outcomes:** conducted for all ARV drugs including DTG and supported by the Botswana-Harvard Partnership. • **Botswana Epidemiological ART Treatment Study Cohort:** established by the Ministry of Health and is prospectively monitoring patients initiating or switching to DTG-containing regimens over three years compared with EFV-containing regimens. • **Research on adverse drug reactions among individuals with TB:** the Botswana National TB Programme is working closely with research partners to monitor any unexpected DTG adverse drug reactions.

Special considerations for children

WHO recommends DTG as alternative first-line ART for adolescents with HIV but does not recommend DTG for children *(2)*. As of June 2016, the United States Food and Drug Administration approved the use of DTG for children six years and older (weighing at least 30 kg), and the European Medicines Agency among children weighing more than 15 kg. Data on the safety of DTG among young children are limited, and few formulations for children are available *(4)*.

However, since the results from ongoing trials are awaited and new formulations for children will become available, active toxicity surveillance for new ARV drugs and formulations for children should be implemented. Prospective cohorts of children in particular have an important role in monitoring both short-term and long-term adverse drug reactions and enable calculation of incidence and analysis of the association between events and risk factors.

3.2 Methods

Active toxicity monitoring of new ARV drugs is based on the following strategic framework: leveraging existing monitoring and evaluation and pharmacovigilance systems, sustainability of the approach, stakeholder engagement and willingness and capacity of ART sites and health-care workers to report and implement the approach. The advantages of using existing monitoring and evaluation and pharmacovigilance structures complemented by a package of tools and training include cost efficiency and improved documentation of clinical practices. Regarding sustainability, the approach will facilitate integration within the ART programme and patient monitoring systems and will apply a standard set of core variables to harmonize data across countries and enable pooled analysis and comparison. Active toxicity monitoring is affordable, feasible and sustainable in settings with limited financial and human resources.

The toxicity of new ARV drugs can be actively monitored in a select number of ART sites within a country based on implementation considerations of feasibility, cost, capacity, resources as well as representativeness. For instance, active toxicity monitoring could be implemented in ART sites that already support a strong monitoring and evaluation programme, since these sites generally have a reliable system for capturing clinical and toxicity data. In addition, the criteria in Box 5 may also assist countries in selecting sites for active toxicity monitoring of new ARV drugs. In some contexts, the geographical distribution of selected ART sites may also be considered if regional representation is a priority for the country.

Box 5. Criteria that may be considered in selecting ART sites for active toxicity monitoring of new ARV drugs

Key criteria for selecting sites for active toxicity monitoring of new ARV drugs

- Number of people initiating DTG or other new ARV drugs: ART sites with the most people initiating or transitioning to DTG or other new ARV drugs
- Availability of electronic medical records: to support data capture and reporting
- Human resource capacity: availability, willingness and commitment as well as capacity of health-care workers to identify, capture and report treatment-limiting toxicity associated with new ARV drugs

Additional criteria that may be considered in selecting sites

- Laboratory monitoring: for detecting, identifying and confirming adverse drug reactions and assessing treatment efficacy
- Managing data and keeping records: availability of unique identifiers, linkage to pharmacy databases and longitudinal patient data, including medication, clinical and adverse drug reaction data
- Ascertaining outcome and following up: following up people receiving new ARV drugs, including key populations, pregnant women and children, and the ability to document outcomes is important, since people lost to follow-up are a source of selection and ascertainment bias in evaluating adverse drug reactions associated with new ARV drugs

3.3 Data collection and reporting

With active toxicity monitoring, health professionals managing individuals initiating new ARV drugs should be required as well as sensitized and trained to report on treatment-limiting toxicity (see the definition section for details). Focusing on specific adverse drug reactions of interest flagged as safety concerns, keeps reporting simple and feasible without compromising quality. WHO has developed a generic adverse drug reaction reporting form for DTG (Annex 1) health workers at ART sites can use to enable standardized reporting of toxicity, drug–drug interactions and relevant comorbidities with data elements that capture various central nervous system adverse drug reactions and immune reconstitution inflammatory syndrome, which have been reported in the literature and linked to the use of DTG or integrase inhibitors. Additional tools and annexes will be produced for other new ARV drugs and will be available to countries for use and adaptation.

Adverse drug reaction reporting form

The following section provides guidance on how to complete the generic DTG adverse drug reaction reporting form for active notification of DTG treatment-limiting toxicity. The notification form should be completed for adults, adolescents and children with treatment-limiting toxicity and immune reconstitution inflammatory syndrome related to DTG use. A maximum of two adverse drug reactions can be reported per form, and each adverse reaction should be reported separately. For individuals with more than two adverse drug reactions, a second DTG adverse drug reaction form should be completed.

Section 1 of the DTG adverse drug reaction reporting form captures demographic data, clinical status and comorbidities as well as details of indication of DTG use and ARV and other drugs at time of onset of the adverse drug reaction.

Figure 4. Section 1 of the reporting form for DTG adverse drug reactions

Name of HIV treatment facility:	Code of reporting site:
	Code of reporting form designed by adverse drug reaction centre:
To facilitate identification should it be necessary to refer back to the patient card	
Patient ID:	Intended to collect risk factors related to clinical status that could be associated with the onset of adverse drug reactions
Date of birth:__/__/____ ☐ Child (<10 years old)	Clinical status when DTG initiated:
	Symptomatic disease ☐Yes ☐No
Sex: ☐Male ☐Female ☐Transgender	Laboratory test results for ART monitoring (if available):
Weight: (kg) Height: (cm)	CD4 cell count at DTG initiation: Date: __/__/____
Case ID number:	Last CD4 cell count: Date: __/__/____ Last viral load (latest): Date: __/__/____

Indication for DTG use:	**Active TB:**
☐ ART initiation (first-line regimen)	☐Yes (date of diagnosis: __/__/____) ☐No
☐ Substitution for EFV or NVP intolerance or toxicity	**Pregnancy:** ☐Yes ☐No ☐Do not know
☐ Third-line regimen	If pregnant: date of last menstrual period: __/__/____
☐ Proactive substitution following introduction of DTG	Gestation week at start of event: (weeks)
☐ Other (specify):	Gestation week at DTG initiation: (weeks)

Applicable to countries that decide to move all individuals on EFV or NVP to DTG first line for programmatic reasons rather than intolerance or toxicity

To disaggregate and enable monitoring of DTG adverse drug reactions among pregnant women and people with TB coinfection for which safety data are currently lacking

Existing comorbidities?

☐ Diabetes	☐ Cardiovascular disease	☐ Hepatitis B coinfection
☐ Hepatitis C coinfection	☐ Renal insufficiency (acute or chronic)	☐ Hepatic insufficiency
☐ Mental disorder (specify):		
☐ Other (specify):		

To identify and capture comorbidities that could be associated with the onset of the reported adverse drug reaction

For reporting the results of laboratory tests performed to assess the adverse drug reaction

Complementary laboratory test results (if available):

ALT: (µmol/L)	AST: (µmol/L)	Other (specify):

ARV or concomitant drugs at the onset of the adverse drug reaction			
Name of ARV drug	Dose	Start date	End date
Other medicines	**Dose**	**Start date**	**End date**

To identify and capture other drugs or drug–drug interactions that could be associated with a reported adverse drug reaction

Section 2 of the DTG adverse drug reaction reporting form collects information on adverse drug reactions, especially focusing on immune reconstitution inflammatory syndrome and central nervous system adverse drug reactions, since these are the most commonly reported adverse drug reactions associated with DTG. Each adverse drug reaction should be reported separately, with a maximum of two reported per notification form. Central nervous system adverse drug reactions are listed and specified to assist health workers with identification and to avoid underreporting. Complementary laboratory test results are also captured in this section to accompany the clinical diagnosis of adverse drug reactions.

Figure 5. Section 2 of the reporting form for DTG adverse drug reactions

The notification form allows up to two adverse reactions to be reported. If there are more than two, complete an additional notification form

Various common central nervous system adverse reactions are specified here to facilitate identification and reporting

Other adverse drug reactions to be reported here

Additional details and clarifications regarding the seriousness of an adverse drug reaction can be reported here

To collect information to assess outcomes associated with various management approaches and generate data to optimally manage DTG adverse drug reactions

Complete separately for each adverse drug reaction. A maximum of two adverse drug reactions per form can be reported.

ADVERSE DRUG REACTION #1

Start date:__/__/____ End date:__/__/____ ☐ Ongoing

NEUROPSYCHIATRIC EVENTS:

- ☐ Abnormal dreams or nightmares
- ☐ Anxiety
- ☐ Confusion or abnormal thinking
- ☐ Depression or mood changes
- ☐ Dizziness, spinning sensation or vertigo
- ☐ Fatigue, tiredness or weakness
- ☐ Insomnia or sleep problems
- ☐ Poor concentration or memory problems
- ☐ Paraesthesia or painful neuropathy
- ☐ Suicide ideation
- ☐ Other (specify):

HYPERSENSITIVITY REACTION:

- ☐ Skin rash/hypersensitivity reaction

HEPATOTOXICITY:

- ☐ Elevated ALT/AST

OTHER ADVERSE DRUG REACTION:

- ☐ Other (specify):

Seriousness of the adverse drug reaction #1

☐ Death	☐ Requires or prolongs hospitalization	☐ Congenital anomaly or birth defect
☐ Life threatening	☐ Disability or permanent damage	☐ Not serious

Remarks:

Adverse drug reaction #1 management:

- ☐ Dose adjustment ☐ Discontinue ARV drug
- ☐ Change regimen: new regimen:__/__/____ Date of changing regimen: __/__/____
- ☐ Other drug used to manage adverse drug reaction (specify):
- ☐ Other (specify):

Results after treating adverse drug reaction #1

☐ Died due to adverse drug reaction ☐ Died not due to adverse drug reaction	☐ Not yet recovering ☐ Recovering	☐ Recovered with sequelae ☐ Recovered without sequelae	☐ Unknown

Figure 5. Section 2 of the reporting form for DTG adverse drug reactions (cont.)

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (see definition at the end of the notification form)	
Did any opportunistic disease occur after the initiation of DTG? ☐ Yes ☐ No	
If YES, check and/or describe:	
☐ Tuberculosis *Date of diagnosis: __/__/____.)*	☐ Cryptococcal meningitis *Date of diagnosis: __/__/____.)*
☐ Cerebral toxoplasmosis *Date of diagnosis: __/__/____.)*	☐ CMV retinitis *Date of diagnosis: __/__/____.)*
☐ Kaposi's sarcoma *Date of diagnosis: __/__/____.)*	
☐ Other (specify):. *Date of diagnosis: __/__/____.)* *Date of diagnosis: __/__/____.)* *Date of diagnosis: __/__/____.)* *Date of diagnosis: __/__/____.)*	

Definition provided to assist health-care workers in identifying conditions associated with immune reconstitution inflammatory syndrome

Section 3 of the DTG adverse drug reaction reporting form captures key information about the health-care worker who completed the form to facilitate data quality review and enable data issues to be followed up and addressed.

Instructions are also provided on the frequency of reporting, date of submission of completed forms and key contact person to whom the notification form should be returned.

Figure 6. Section 3 of the reporting form for DTG adverse drug reactions

Section 3: Reporting instructions

Completed by:		Title:	
Email:		Telephone:	
Signature:		Date of reporting: __/__/____	
Please report even if: You are not certain the product caused the event OR you do not have all the details			
Person to report: Doctor, pharmacist or nurse			
Time to report: All reporting forms should be completed as soon as possible and sent to XXX by day XX every month. The designated personnel will enter the data in the designed spreadsheet and send to xxx by the xxth day of every month.			
Who to send it to: Name:	Tel.:	Fax:	Email:
For more information, contact: Name:	Tel.:	Fax:	Email:

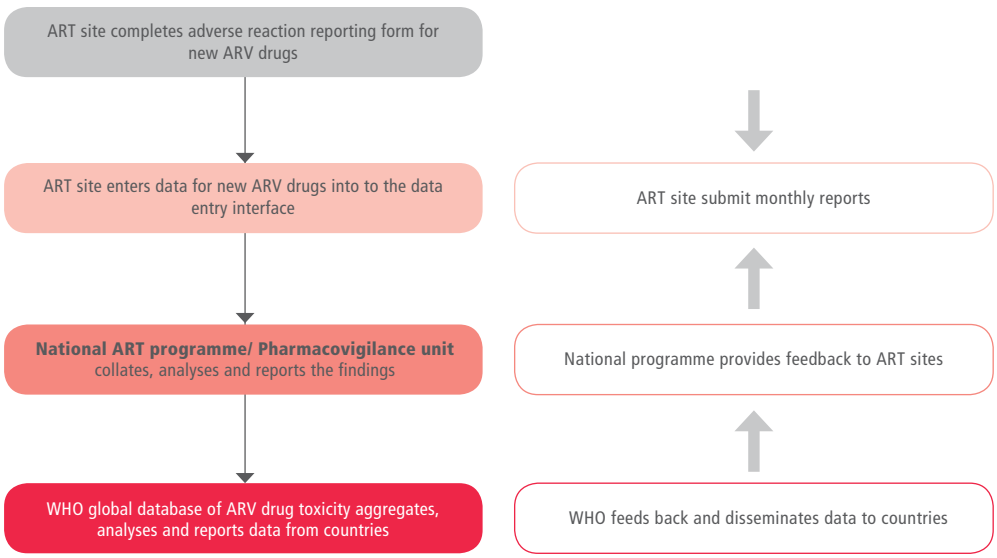
In addition to the above, countries may also consider conducting clinical record review for individuals for whom a new ARV drug has been discontinued or substituted without a documented reason to augment the data collected using adverse drug reaction reporting tools such as the one above. The use of this complementary data capture approach is a decision to be taken at the country level based on considerations of feasibility and available resources, including cost and the burden on health-care workers.

Box 6. Summary of data collection and reporting for active toxicity monitoring of new ARV drugs

- All health-care professionals involved in patient care are sensitized and required to ask about and investigate serious adverse drug reactions associated with new ARV drugs at every encounter as part of routine patient care.
- Serious adverse drug reactions include an adverse reaction that can cause death or life-threatening illness, requires hospitalization, leads to disability, congenital anomaly or birth defect, leads to treatment interruption or requires changing drug or regimen.
- A standardized reporting form is available for ART sites to use to report adverse drug reactions to DTG (Annex 1).
- The reporting form is supported by specific guidance (data dictionary and training materials) on when to complete them and with details of codes to be used for standardized reporting of adverse drug reactions.
- Reporting lasts the whole length of treatment.
- The reporting burden on health-care workers is reduced by focusing on one drug and targeted adverse drug reactions.
- All reporting sites should enter all completed reported forms into an electronic database for aggregation and analysis (see section 3.3 on data management).

Fig. 7 summarizes the data collection and reporting flow between the levels involved in active toxicity monitoring of new ARV drugs. Reports should be submitted on a monthly basis by the selected ART sites, and the national ART programme or pharmacovigilance unit should collate, analyse and feedback findings to the sites.

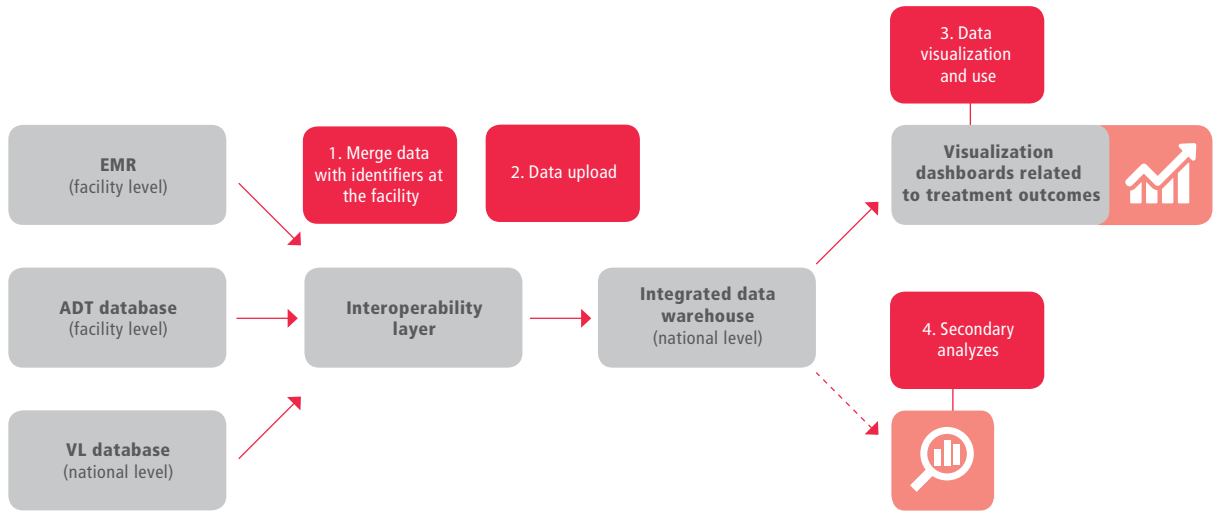
Figure 7. Data collection and reporting process for active toxicity monitoring for new ARV drugs



Box 7. Monitoring of new ARV uptake and clinical outcomes, including adverse drug reactions, using routinely collected data in Kenya

The Enhanced Data System (EDS) in Kenya triangulates routinely collected data from clinical, laboratory and pharmacy databases to enable real-time monitoring of key indicators related to introducing new ARV drugs, including adverse drug reactions and patient outcomes. In collaboration with the National AIDS and STI Control Programme (NASCOP) and Palladium, ICAP at Columbia University is supporting the EDS by developing an interoperability layer to link clinical data from electronic medical records with ART dispensing information from the ART Dispensing Tool and the viral load data from the national viral load database. The resulting complete patient record will be deidentified and uploaded to the EDS database in the Integrated National Data Warehouse. A dashboard that enables the visualization of specific indicators to monitor the prescribing practices and clinical outcomes of people receiving new ARV drugs will be developed with support from ICAP at Columbia University and will be accessible to various stakeholders (Fig. 8). To strengthen toxicity monitoring, an adverse drug reaction screening form has also been developed (Fig. 9) and will be integrated into the electronic medical records. Currently, 24 facilities have been targeted to pilot the EDS and the use of the adverse drug reaction form with the aim of scaling this system nationwide. Training materials to build the capacity of health-care providers to transition people to new ARV drugs and monitor the occurrence of adverse events and clinical outcomes have been developed and are currently in use at the targeted enhanced monitoring facilities.

Figure 8. Data management and reporting of routinely collected data on ARV uptake and clinical outcomes including adverse drug reactions in Kenya



ADT: ARV Dispensing Tool; VL: viral load; EMR: electronic medical record.

Figure 9. Screening checklist for adverse drug reaction symptoms from ARV drugs from Kenya

Adverse drug reaction / Adverse effects screening form				
Patient Details as in EMR	Visit Date: __/__/____			
ART regimen: ☐ TLE600 ☐ TLE400 ☐ Use of DTG based ART ☐ ART initiation (1st line regimen) ☐ Substitution for EFV intolerance/toxicity ☐ Substitution for NVP ☐ 3rd line regimen ☐ Substitution for ATV/r in PWID ☐ Substitution for PI/r in 2nd line with TB disease ☐ Other (specify): ☐ TLD as FDC				
Symptom Screen Section after ART initiation				
Symptom	**Did you experience any of the following symptoms since ART initiation?** (Indicate Yes or No)	**Are you currently experiencing the symptom?** (Indicate Yes or No)	**Adherence Have you ever skipped a dose due to these symptoms?** (Indicate Yes or No)	**Severity of the symptom indicate as:** ☐ Mild (Grade 1) ☐ Moderate (Grade 2) ☐ Severe (Grade 3) ☐ Life threatening (grade 4)
Abnormal dreams or nightmares (Frightening or unpleasant dreams)				
Anxiety				
Confusion/abnormal thinking				
Depression/mood changes (frequently feeling very low)				
Dizziness/spinning sensation/vertigo				
Fatigue/tiredness/weakness				
Insomnia (lacking sleep at night/sleep problems)				
Poor concentration/memory problems				
Burning and tingling in limbs/Paresthesia/painful neuropathy				
Suicide ideation (thoughts on ending the life)				
Skin rash/hypersensitivity reaction				
Abdominal discomfort/abdominal pain				
Nausea/vomiting				
Diarrhoea				
Jaundice				
Fat changes/ lipodystrophy/lipohypertrophy				
Gynaecomastia				
Headache				
Anaemia/pancytopenia				
Renal failure/renal insufficiency				
Other. Specify:				
Immediate action taken:	☐ Regimen changed	☐ Regimen not changed		☐ Regimen stopped
Other actions taken:	☐ Labs requested. Specify			
Outcome (Results after ADRI):	☐ Recovering/resolving	☐ Requires or prolongs hospitalization		☐ Recovered/resolved
	☐ Caused a congenital anormaly	☐ Requires intervention to prevent permanent damage		☐ Died due to ADR
	☐ Died not due to ADR			
Please report even if: You are not certain the product caused the event OR you don't have all the details.				

3.4 Data management and analysis

Data on adverse drug reactions related to the use of new ARV drugs collected at the facility level on paper forms should be entered into a specifically designed electronic database to facilitate data analysis. WHO has developed a data dictionary (Annex 3) matched to the generic DTG adverse reaction reporting form that countries can adapt and use as needed. This will be expanded to incorporate other new ARV drugs and made available to countries.

The national ART programme should oversee and coordinate data management. Entering the data from all reports of toxicity related to new ARV drugs into the same electronic database will facilitate the pooling of data and analysis of aggregate data on treatment-limiting toxicity associated with new ARV drugs. The database can be used to generate reports providing the frequencies of adverse drug reactions, demographic data, descriptive analysis of the management and outcomes of adverse drug reactions.

3.5 Data confidentiality and ethical considerations

Maintaining data security and safeguarding the confidentiality of patient information is paramount. The personnel involved in reporting should be trained and provided standard operating procedures on data security measures and protecting the confidentiality of client information. Access to completed adverse drug reaction reporting forms for new ARV drugs should be limited from scrutiny by unauthorized people. All computer systems used, including the data entry interface programme for reporting treatment-limiting toxicity, should be controlled with passwords at the entry and analysis level. Published data, including reports, should not contain any patient-identifying information and should be deidentified before aggregation at the national level.

Monitoring the toxicity and safety of new ARV drugs is an integral part of HIV patient monitoring and the adoption of new drugs within HIV treatment programmes. Active toxicity monitoring of DTG and other new ARV drugs will develop much needed local data to improve patient management and should be presented to ethics review committees as such should ethics approval be required. Active toxicity monitoring is not a clinical trial or study and thus will not interfere with patient management but rather aims to collect data to guide decision-making on the safety of newly introduced ARV drugs in the interest of public health.

3.6 Reviewing and controlling data quality

The quality of the data and various processes used to establish data quality influence the effective use of data for decision-making. Good-quality data not only contribute to monitoring the safety of new ARV drugs but also help to improve patient care and management. The following measures are suggested to improve data quality and control related to active toxicity monitoring of new ARV drugs.

- The personnel involved in collecting and collating data should have these functions included in their terms of reference and be allocated time to complete these activities. A data flow chart that describes how and when various information is collected and reported, the people responsible, the formats used and the timing of each step provides clarity to the data collection process.
- The personnel involved in data collection, including supervisors, should receive instructions and training and be evaluated in using the formats and record-keeping.
- Supervisors should regularly review the adverse drug reaction reporting forms to ensure that they are filled out correctly and completely.
- Quality assurance and use of toxicity monitoring data should be included as part of routine supervisory assessments and as an aspect of service quality at the ART site. For sites using electronic medical records, data quality should be routinely assessed comparing paper-based reports with electronic medical records.
- Whenever possible, adverse reactions related to new ARV drugs should be recorded at the time of the patient encounter rather than recorded later from memory.
- Electronic medical records and a database should be used to capture and manage data.
- The adverse drug reaction reporting forms should be archived systematically to allow for verification or record review to confirm aggregated results, as needed.
- ARV toxicity data have inherent value and should be available for use and analysis locally (such as at the site level) to improve the management of adverse drug reactions instead of being reported up for higher-level or central-level use only.

Box 8. Data quality measures implemented in Brazil for active DTG toxicity monitoring

After DTG was introduced in Brazil, by November 2017 about 73 000 adults were receiving DTG, of which 90% (41 566 as first-line ART and 23 811 as third-line ART) were followed up and actively monitored for adverse drug reactions. To ensure data quality, mandatory data are reviewed, non-tabulated fields are excluded and data checks are carried out.

1. **Mandatory reporting of specific data elements and building data validation rules into the database system.** For instance, when clinical manifestations of immune reconstitution inflammatory syndrome are reported, entering the start date and either an end date or the option of persistent manifestation is mandatory in the online database, and a data validation rule is built into the system to ensure that this is reported. This is also the case for the start and end date and the persistence of adverse drug reactions.
2. **Providing specific options to be selected from a drop-down list.** To facilitate reporting and analysis, reporting options are provided that are selected from a list rather than allowing respondents to indicate "other" and using free text to report. Specifically, after the data for the clinical status before initiating DTG were reviewed, the option of selecting "other" with the respondent specifying the condition was removed, since this led to significant variability in responses and data quality issues that made analysis difficult.
3. **Identifying a reporter to facilitate the follow-up of information for further analysis.** The adverse drug reaction questionnaire included the possibility of indicating who completed the information: doctor, nurse, patient, pharmacist or other pharmacy professional. Patients can also complete questionnaires with paper versions available for distribution so they can record adverse drug reactions and start dates as they occur and submit them to health-care workers at their next appointment.
4. **Regularly assessing data quality.** An evaluation meeting on data was completed during the first three months after active toxicity monitoring was introduced for the entire country with supervisors from regions.

3.7 Dissemination and data use

Site-level data should be forwarded to the national level (ART programme, health ministry), where they are aggregated and analysed and reports generated regularly (such as quarterly) and disseminated. Data should also be fed back to ART sites to guide and provide information on managing adverse drug reactions related to new ARV drugs to improve patient outcomes. If cases in which adverse drug reactions could have been prevented are identified, non-punitive feedback should be provided to the ART site and caregiver.

Communication between reporting levels should be bidirectional; just as systems for reporting data to higher reporting levels are established, so should feedback and data analysis flow regularly back down (Fig. 7). Feedback mechanisms should be strategically designed to enable this. This can include approaches such as establishing telephone help lines to provide information and advice to health-care workers on optimally managing adverse drug reactions related to ARV drugs, which have been successfully used in South Africa *(20)*.

Further, effectively using data on the toxicity of new ARV drugs requires it to be available in real time when decisions are made. Ultimately, the data collected through active toxicity monitoring should provide much-needed information to the national ART programme on the frequency and severity of adverse drug reactions associated with new ARV drugs as well as information to guide the management of drug toxicity in the context of actual use within the national programme.

WHO, in its role as the global convenor in ARV toxicity monitoring, will provide technical assistance in the form of tools, training materials and an electronic database to support countries in implementing active toxicity monitoring of new ARV drugs. Countries are urged to share and report toxicity data for all new ARV drugs, including DTG. By doing so, contributing countries ensure that the information collected at their national level can also be used for more general safety surveillance at the global level. WHO, in turn, will collate, analyse and report such data. Global dissemination of results will enable greater clarity on the safety profile of DTG and other new ARV drugs to support safe and appropriate use.

3.8 Stakeholders' engagement, roles and responsibilities

Successfully implementing active toxicity monitoring for new ARV drugs requires the active engagement of all relevant stakeholders at every level. The national ART programme and health ministry will take overall leadership for implementation and will identify and engage other key stakeholders. Table 6 describes the roles and responsibilities of key stakeholders.

Table 6. Roles and responsibilities of key stakeholders in monitoring the toxicity of new ARV drugs

Stakeholder	Roles and responsibilities
ART site	
Health-care workers (completing and submitting data forms)	✔ Overall responsibility for monitoring adverse drug reactions related to new ARV drugs and timely documentation using standardized data reporting forms and submission **Required elements:** • Standardized adverse drug reaction reporting forms available • Training and feedback for health-care workers on managing adverse drug reactions and reporting
Data entry clerk or operator (inputting data)	✔ Enter and submit data from paper data collection forms into the electronic database and ensure data security **Required elements:** • Standardized data entry interface programme • Training, supervision and feedback on data quality
National ART programme /pharmacovigilance unit, ministry of health	
Monitoring and evaluation/ pharmacovigilance focal point (data analysis and dissemination)	✔ Review data reports on adverse drug reactions to new ARV drugs and risk factors and assess and support data quality ✔ Aggregate data and generate regular quarterly or annual reports ✔ Disseminate and feedback information to relevant stakeholders, including reporting ART sites **Required elements:** • National database with data aggregation and report generation features • Training • Standard operating procedures for data quality assurance
ART programme manager (data use)	✔ Review reports of adverse drug reactions related to new ARV drugs ✔ Develop recommendations to address findings and toxicity issues identified by the toxicity monitoring of new ARV drugs ✔ Promote the dissemination and communication of priority public health recommendations, including changes to the ART programme emerging from the toxicity monitoring data as required **Required elements:** • Timely reports summarising available data on new ARV related adverse drug reactions and risk factors • Effective communication channels
Other stakeholders	
Partners (technical and financial support)	✔ Provide technical and financial assistance to support countries in implementing the toxicity monitoring of new ARV drugs
WHO (coordination and technical support)	✔ Provide normative guidance, tools, training materials and technical support to key countries ✔ Convene partners to support the implementation of active toxicity monitoring

3.9 Training

Ongoing training and mentoring is critical for effective implementation of active toxicity monitoring of new ARV drugs. All relevant personnel at the selected ART sites should be trained beforehand on the purpose and objectives of active toxicity monitoring, how to identify relevant adverse drug reactions and how to record them in the data collection tools. To this end, WHO is developing additional training resources, including a slide set on the active toxicity monitoring approach for new ARV drugs, that countries can use and adapt as needed. The slide set will cover routine and active toxicity monitoring of new ARV drugs, including rational and methods, data collection and reporting and data quality assurance. In addition, the quality assurance and mentoring procedures implemented should include regular visits to participating sites by designated personnel from the national ART programme.

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ANNEX 1.

Reporting form for dolutegravir adverse drug reactions and/or immune reconstitution inflammatory syndrome in adults, adolescents and children

(This form is to be adapted and used within the national HIV programme and targeted programme for monitoring ARV drug toxicity)

Information will be kept confidential

Name of HIV treatment facility:	Code of reporting site: Code of reporting form designed by adverse drug reaction centre:
Patient ID:	Clinical status when DTG initiated:
Date of birth:__/__/____ ☐ Child (<10 years old)	Symptomatic disease ☐Yes ☐No
Sex: ☐Male ☐Female ☐Trangender	Laboratory test results for ART monitoring (if available):
Weight: (kg) Height: (cm)	CD4 cell count at DTG initiation: Date: __/__/____
Case ID number:	Last CD4 cell count: Date: __/__/____ Last viral load (latest): Date: __/__/____

Indication for DTG use:	**Active TB:**
☐ ART initiation (first-line regimen)	☐Yes (date of diagnosis: __/__/____) ☐No
☐ Substitution for EFV or NVP intolerance or toxicity	Pregnancy: ☐Yes ☐No ☐Do not know
☐ Third-line regimen	If pregnant: date of last menstrual period: __/__/____
☐ Proactive substitution following introduction of DTG	Gestation week at start of event: (weeks)
☐ Other (specify):	Gestation week at DTG initiation: (weeks)

Existing comorbidities?		
☐ Diabetes	☐ Cardiovascular disease	☐ Hepatitis B coinfection
☐ Hepatitis C coinfection	☐ Renal insufficiency (acute or chronic)	☐ Hepatic insufficiency
☐ Mental disorder (specify):.		
☐ Other (specify):		

Complementary laboratory test results (if available):		
ALT: (µmol/L)	AST: (µmol/L)	☐Other (specify):

ARV or concomitant drugs at the time of adverse drug reaction onset			
Name of ARV drug	Dose	Start date	End date
Other medicines	Dose	Start date	End date

Complete separately for each adverse drug reaction.
Maximum of 2 adverse drug reactions per form can be reported.

ADVERSE DRUG REACTION #1

Start date:__/__/____ End date:__/__/____ ☐ Ongoing

NEUROPSYCHIATRIC EVENTS:

- ☐ Abnormal dreams or nightmares
- ☐ Anxiety
- ☐ Confusion or abnormal thinking
- ☐ Depression or mood changes
- ☐ Dizziness, spinning sensation or vertigo
- ☐ Fatigue, tiredness or weakness
- ☐ Insomnia or sleep problems
- ☐ Poor concentration or memory problems
- ☐ Paraesthesia or painful neuropathy
- ☐ Suicide ideation
- ☐ Other (specify):

HYPERSENSITIVITY REACTION:

- ☐ Skin rash/hypersensitivity reaction

HEPATOTOXICITY:

- ☐ Elevated ALT/AST

OTHER ADVERSE DRUG REACTION:

- ☐ Other (specify):

Seriousness of the adverse drug reaction #1

☐ Death	☐ Requires or prolongs hospitalization	☐ Congenital anomaly or birth defect
☐ Life threatening	☐ Disability or permanent damage	☐ Not serious

Remarks:

Adverse drug reaction #1 management:

☐ Dose adjustment	☐ Discontinue ARV drug
☐ Change regimen: new regimen:_____/_____/_____	Date of changing regimen: __/__/____

☐ Other drug used to manage adverse drug reaction (specify):

☐ Other (specify):

Results after treating adverse drug reaction #1

☐ Died due to adverse drug reaction	☐ Not yet recovering	☐ Recovered with sequelae	☐ Unknown
☐ Died not due to adverse drug reaction	☐ Recovering	☐ Recovered without sequelae	

Leave section blank if only one adverse drug reaction has been observed. Complete separately for each adverse drug reaction.
A maximum of two adverse drug reactions per form can be reported.

ADVERSE DRUG REACTION #2

Start date:__/__/____ End date:__/__/____ ☐ Ongoing

NEUROPSYCHIATRIC EVENTS:

- ☐ Abnormal dreams or nightmares
- ☐ Anxiety
- ☐ Confusion or abnormal thinking
- ☐ Depression or mood changes
- ☐ Dizziness, spinning sensation or vertigo
- ☐ Fatigue, tiredness or weakness
- ☐ Insomnia or sleep problems
- ☐ Poor concentration or memory problems
- ☐ Paraesthesia or painful neuropathy
- ☐ Suicide ideation
- ☐ Other (specify):

HYPERSENSITIVITY REACTION:

- ☐ Skin rash/hypersensitivity reaction

HEPATOTOXICITY:

- ☐ Elevated ALT/AST

OTHER ADVERSE DRUG REACTION:

- ☐ Other (specify):

Seriousness of the adverse drug reaction #2

☐ Death	☐ Requires or prolongs hospitalization	☐ Congenital anomaly or birth defect
☐ Life threatening	☐ Disability or permanent damage	☐ Not serious

Adverse drug reaction #2 management:

☐ Dose adjustment	☐ Discontinue ARV drug
☐ Change regimen: new regimen:_____/_____/_____	Date of changing regimen: __/__/____

☐ Other drug used to manage adverse drug reaction (specify):

☐ Other (specify):

Results after treating adverse drug reaction #2

☐ Died due to adverse drug reaction	☐ Not yet recovering	☐ Recovered with sequelae	☐ Unknown
☐ Died not due to adverse drug reaction	☐ Recovering	☐ Recovered without sequelae	

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME
(see definition at the end of the notification form)

Did any opportunistic disease occur after the initiation of DTG? ☐ Yes ☐ No

If YES, check and/or describe:

☐ Tuberculosis *Date of diagnosis: __/__/____)*	☐ Cryptococcal meningitis *Date of diagnosis: __/__/____.)*
☐ Cerebral toxoplasmosis *Date of diagnosis: __/__/____)*	☐ CMV retinitis *Date of diagnosis: __/__/____.)*
☐ Kaposi's sarcoma *Date of diagnosis: __/__/____)*	

☐ Other (specify):

_____ *Date of diagnosis: __/__/____)*

_____ *Date of diagnosis: __/__/____)*

_____ *Date of diagnosis: __/__/____)*

_____ *Date of diagnosis: __/__/____)*

Completed by:	Title:
Email:	Telephone:
Signature:	Date of reporting: __/__/____.

Please report even if:
You are not certain the product caused the event OR you do not have all the details

Person to report:
Doctor, pharmacist or nurse

Time to report:
All reporting forms should be completed as soon as possible and sent to XXX by day XX every month. The designated personnel will enter the data in the designed spreadsheet and send to xxx by the xxth day of every month.

Who to send it to:			
Name:	Tel.:	Fax:	Email:
For more information, contact:			
Name:	Tel.:	Fax:	Email:

Important information

- A serious adverse drug reaction is an adverse reaction that can cause one of the following consequences: limiting treatment, death, life threatening, requires or prolongs hospitalization, disability or permanent damage, congenital anomaly or birth defect.
- A case that leads to treatment interruption or requires changing drug or regimen because of an adverse drug reaction is also considered a serious adverse drug reaction.

Common toxicity, adverse reaction	Management
Central nervous system or mental symptoms (insomnia, sleep problems, anxiety, depression)	Central nervous system or mental symptoms are usually mild and subside within a few weeks after initiation.
Skin hypersensitivity reactions	Skin hypersensitivity reactions or persistent central nervous system or mental adverse reactions: replace with another therapeutic class (efavirenz or boosted protease inhibitors).
Immune reconstitution inflammatory syndrome[a]	Managing immune reconstitution inflammatory syndrome includes treating the emergent infection, continuing ART and supportive measures as needed. Use of corticosteroids can be considered in some situations. Central nervous system immune reconstitution inflammatory syndrome can be a life-threatening condition and frequently needs urgent care and support.

[a]Definition of immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome describes a collection of infectious or inflammatory conditions associated with paradoxical clinical worsening of pre-existing infectious processes caused by the host's regained capacity to mount an inflammatory response after people living with HIV initiate antiretroviral therapy (ART). It usually occurs in the first two months after starting ART among people living with HIV with severe immunodeficiency and rapid immune recovery (rapid increase in CD4 counts and viral load suppression). Immune reconstitution inflammatory syndrome can present clinically in two types. The first is called unmasked immune reconstitution inflammatory syndrome because of occult and subclinical opportunistic infection and a generally detectable pathogen. The second is called paradoxical immune reconstitution inflammatory syndrome and is characterized by recrudescence or relapse of infection successfully treated previously and marked antigen-induced immune activation with no or few detectable pathogens.

Source: Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations. Geneva: World Health Organization; 2017

ANNEX 2.

Example of dolutegravir adverse reaction reporting form: Brazil

Pharmacovigilance questionnaire on use of dolutegravir 50 mg

1. Full name:	**2.** Register number:
3. Social name:	**4.** Social security number: ☐☐☐☐☐☐☐☐☐☐☐
5. Date of birth: __/__/____	**6.** Mother's name:

7. Was there a suspected adverse reaction after the start of the treatment regimen containing dolutegravir?

☐Yes ☐No ☐After pharmaceutical advice on the importance of information for patient follow-up, the patient declined to respond.

8. What adverse reaction (s) did the patient present and what were the dates at the beginning of each reaction? Report the undesirable symptom(s) presented after the use of the dolutegravir-containing treatment regimen.

Adverse reaction:	Estimated date of adverse reaction initiation (Inform DD/MM/YY or at least MM/YY)

9. Severity of adverse reaction:

- ☐ The reaction was life threatening
- ☐ The reaction caused patient hospitalization
- ☐ The reaction prolonged the patient hospitalization time
- ☐ The reaction caused persistent or severe patient disability
- ☐ The reaction did not cause any of the above consequences but was considered severe
- ☐ The reaction was not considered severe

10. Patient clinical data before using dolutegravir. Check the diseases presented by the patient:

- ☐ Diabetes
- ☐ Cardiovascular disease
- ☐ Hepatitis B coinfection
- ☐ Hepatitis C coinfection
- ☐ Renal insufficiency (acute or chronic)
- ☐ Hepatic insufficiency
- ☐ Mental disorder
- ☐ Other (describe)

11. Considering that immune reconstitution inflammatory syndrome can occur among people with advanced HIV infection who started antiretroviral therapy (ART) and that the definition of an immune reconstitution inflammatory syndrome case includes the occurrence of clinical deterioration due to infectious or inflammatory condition after onset of ART, associated with signs and symptoms that cannot be explained by another infection or neoplasm, treatment failure for opportunistic infection, adverse reaction to drugs or lack of adherence to ART or treatment for tuberculosis. The clinical presentation of immune reconstitution inflammatory syndrome can be of two types: the first is called unmasked immune reconstitution inflammatory syndrome, because it is characterized by occult and subclinical opportunistic infection and with a generally detectable pathogen; The second is called paradoxical immune reconstitution inflammatory syndrome and is characterized by recrudescence or relapse of infection successfully treated previously and marked antigen-induced immune activation with no or few detectable pathogens. Clinically, it can be expressed by onset or enlargement of lymph nodes, fever, weight loss, worsening of respiratory and radiological symptoms. Central nervous system immune reconstitution inflammatory syndrome can be life-threatening and frequently requires urgent care.

Has the patient presented any characteristic reaction to immune reconstitution inflammatory syndrome? If yes, describe the clinical manifestations:

Immune reconstitution inflammatory syndrome clinical sign or symptom:	Estimated date of adverse reaction initiation (report DD/MM/YY or at least MM/YY)

12. Previous opportunistic disease exacerbated after the onset of dolutegravir? ☐Yes ☐No

If YES, check and/or describe:

- ☐ Oral candidiasis persisting for more than two months
- ☐ Cytomegalovirus (CMV) infection
- ☐ Herpes zoster, with two or more episodes or affecting more than one dermatome
- ☐ Extrapulmonary cryptococcosis
- ☐ Pneumonia
- ☐ Cerebral toxoplasmosis
- ☐ Kaposi's sarcoma
- ☐ Tuberculosis
- ☐ Atypical mycobacteriosis
- ☐ Other:

13. Active opportunistic disease? ☐Yes ☐No

If YES, check and/or describe: _____

14. Other medicines used while using the dolutegravir-containing regimen. Cite the other medicines used by the patient including herbal products, multivitamins and food supplements (do not mention ARV drugs): _____

ANNEX 3.

Data dictionary for adverse drug reaction reporting form for dolutegravir

FACILITY INFORMATION					
Question code	**Question Name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
COUNTRY	Country	Country of the primary source	Char		
SITENAM	Facility name	Name of the primary source (HIV treatment facility)	Char		
SITEID	Site identifier	Site ID number (code of reporting site)	Char		
DICTNAM[a]	Coding use for AE/SAE terminology	Dictionary name used by the facility for coding of AE terms	Category	1	MedDRA
				2	WHOART
				3	Other scale (specify)
				4	None

[a] Optional data. This information may be extracted from the site description form.

PATIENT DEMOGRAPHICS, DETAILS AND KEY DATA OF MEDICAL HISTORY					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
SUBJID	Patient ID	Patient ID number	Char		
BRTHDTC	Date of birth	Birth date in format (DD-MMM-YYYY)	Date		
PEDFLAG	Child	Indicates whether this is report for a patient younger than 10 years old	Category	Y	Yes
SEX	Gender	Patient's sex	Category	F	Female
				M	Male
				TG	Transgender
				U	Unknown
WEIGHT	Weight	Patient weight in kg	Num		
HEIGHT	Height	Patient height in cm	Num		
CLINST	Clinical status at time of DTG initiation	Indicates whether the patient has symptomatic HIV disease at time of DTG initiation	Category	N	No
				U	Unknown
				Y	Yes
CD4CTIN	CD4 cell count at DTG initiation	CD4 cell count (at time of DTG initiation)	Num		
CD4CTINDTC	Date of CD4 cell count at DTG initiation	Date of CD4 cell count at DTG initiation (DD-MMM-YYYY)	Date		
CD4CTLA	CD4 cell count last	CD4 cell count (latest available)	Num		
CD4CTLADTC	Date of last CD4 cell count	Date of CD4 cell count (latest available) (DD-MMM-YYYY)	Date		
VIRLOLA	HIV viral load last	HIV viral load (latest available)	Num		
VIRLOLADTC	Date of latest HIV viral load	Date of HIV viral load (latest available) (DD-MMM-YYYY)	Date		

PATIENT DEMOGRAPHICS, DETAILS AND KEY DATA OF MEDICAL HISTORY					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
DTGINDIC	Indication for DTG	Indication for DTG use	Category	1	ART initiation (first-line treatment)
				2	Substitution for EFV or NVP intolerance or toxicity
				3	Third-line regimen
				4	Proactive substitution following introduction of DTG
				8	Other
				9	Unknown
DTGINDICOTH	Indication for DTG – other	Other indication for DTG use (if "other" was selected under "Indication for DTG use")	Char		
PCONFIND	Pregnancy status at start of event	Indicates whether the patient was pregnant at the time of the onset of adverse drug reaction	Category	N	No
				NA	Not applicable
				U	Unknown
				Y	Yes
LMPSTDTC	If pregnant, date of last menstrual period	Start date of last menstrual period (The first day of the most recent menstrual cycle) (DD-MMM-YYYY)	Date		
EGESTAGE	If pregnant, gestation week at start of event	Estimated gestational age (expressed in weeks) at the start of the event (an approximate calculation of the gestational age of the fetus at the start of the event)	Num		
DGTGESTAGE	If pregnant, gestation week at DTG initiation	Estimated gestational age (expressed in weeks) at the time of DTG initiation (an approximate calculation of the gestational age of the fetus at the start of the treatment with DTG).	Num		
TBACT	Active tuberculosis	Indicate whether the patient presents with active TB	Category	N	No
				U	Unknown
				Y	Yes
TBDIAGDT	Date of TB diagnosis	Date of TB diagnosis, if active TB is reported (DD-MMM-YYYY)	Date		
MHDIAB	Comorbidity – diabetes	Indicate whether the patient has diabetes	Category	Y	Yes
MHCARD	Comorbidity – cardiovascular disease	Indicate whether cardiovascular disease is a comorbidity for this patient	Category	Y	Yes
MHHEPB	Comorbidity – hepatitis B coinfection	Indicate whether the patient has hepatitis B coinfection	Category	Y	Yes
MHHEPC	Comorbidity – hepatitis C coinfection	Indicate whether the patient has hepatitis C coinfection	Category	Y	Yes
MHRENINS	Comorbidity – renal insufficiency	Indicate whether the patient has acute or chronic renal insufficiency	Category	Y	Yes
MHHEPINS	Comorbidity – hepatic insufficiency	Indicate whether the patient has acute or chronic hepatic insufficiency	Category	Y	Yes

MEDICAL HISTORY – OTHER EXISTING COMORBIDITIES					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
MHTERM1	Verbatim comorbidities – mental disorder	Describe the relevant mental disorder that represents existing comorbidities	Char		

MEDICAL HISTORY – OTHER EXISTING COMORBIDITIES					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
MHDECOD1	Coding comorbidity (mental disorders)	Dictionary-derived text description of MHTERM1. Equivalent to the Preferred Term (PT in MedDRA)	Char		
MHTERM2	Verbatim comorbidities – other	Describe other existing comorbidities	Char		
MHDECOD2	Coding comorbidities (others)	Dictionary-derived text description of MHTERM2. Equivalent to the Preferred Term (PT in MedDRA)	Char		

Note: the medical history section can be replicated as many times as needed to record all existing comorbidities reported in the report under "mental disorder (specify)" and "other comorbidities (specify)".

LABORATORY ASSESSMENTS Results of laboratory tests performed at the time of adverse drug reaction					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
LBTEST	What is the lab test name?	Indicate the test name of the laboratory test performed for the investigation of the patient	Char		
LBDTC	Date when lab test is done	Date of test in format (DD-MMM-YYYY)	Date		
LBORRES	Result	Result of the laboratory test, as originally received or collected	Num		
LBORRESU	Unit	Units	Char		
LBORNRLO	Normal low range	Lower limit normal	Num		
LBORNRHI	Normal high range	Upper limit normal	Num		

Note: the laboratory assessment section can be replicated as many times as needed to record all adverse drug reactions reported in the report. This section includes the results of laboratory tests for ALT and AST recorded on the DTG adverse drug reaction reporting form..

MEDICAL TREATMENTS (ARV drugs and other medicines as concomitant treatments) The treatment to be reported is the one taken by the patient at the time the adverse drug reaction onset					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
EXCOLLECT	Drug name	Name of the treatment as originally received or collected	Char		
EXTRT	String to be coded	Name of the treatment in a coded format defined	Char		
EXDOSE	Daily dose	Total dose taken per day	Num		
EXDOSU	Dose (unit)	Record the unit of dose or amount taken per period recorded (such as ng, mg or mg/kg)	Category	Using CDISC terms	
EXDOSFRQ	Frequency (as days per weeks)	Record the frequency the study treatment was administered in days per week	Num		
EXROUTE	Route of administration	Record the route of administration (such as IV, oral, transdermal)	Category	Using CDISC terms	
EXSTDTC	Drug start date	Date when administration of the treatment began (DD-MMM-YYYY).	Date		
EXENDTC	Drug stop date	Date when administration of the treatment ended (DD-MMM-YYYY).	Date		
EXONGO	Drug still ongoing	Indicates whether the drug is still ongoing. It is expected that every reported drug should have either an end date or the ongoing field marked "yes", but not both	Category	N	No
				NA	Not applicable
				U	Unknown
				Y	Yes

ADVERSE DRUG REACTION DESCRIPTION (listed one by one)					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
AEID	Local adverse event case identifier	Adverse drug reaction case ID in local database (case ID number on reporting form)	Char		
AEWID	Worldwide unique case identification number	International unique adverse drug reaction case identifier for the ICSR. If not provided by transferring site, then leave blank	Char		
AETERM1	Adverse events diagnosis (specific events)	Select the event presented by the patient (one at a time)	Category	1	Abnormal dreams or nightmares
				2	Anxiety
				3	Confusion or abnormal thinking
				4	Depression or mood changes
				5	Dizziness, spinning sensation or vertigo
				6	Fatigue, tiredness or weakness
				7	Insomnia or sleep problems
				8	Paraesthesia or painful neuropathy
				9	Suicide ideation
				10	Skin rash or hypersensitivity reaction
				11	Elevated ALT/AST (hepatotoxicity)
				12	Other neuropsychiatric events
				13	Other (non-neuropsychiatric event)
AETERM4	Other adverse events diagnosis (in English)	Verbatim (investigator-reported term) description of the adverse drug reaction in English if adverse drug reaction is not listed on the form	Char		
AEDECOD	Adverse event coding	Dictionary-derived text description of AETERM. Equivalent to the Preferred Term (PT in MedDRA)	Char		
AESTDTC	Start date	Record the start date of the adverse drug reaction using this format (DD-MMM-YYYY)	Date		
AEENDTC	Event end date	Record the date that the adverse drug reaction resolved or led to death using this format (DD-MMM-YYYY). If the adverse drug reaction is ongoing, this field should be blank	Date		
AEONG	Adverse event ongoing	Indicates whether the adverse drug reaction is still ongoing. If the adverse drug reaction has an end date, leave blank	Category	1	Yes
AESTDTH	Serious adverse drug reaction: death	Indicates "Yes" if the adverse drug reaction resulted in death	Category	Y	Yes
AESLIFE	Serious adverse drug reaction: life threatening	Indicates "Yes" if the adverse drug reaction was life threatening	Category	Y	Yes
AESHOSP	Serious adverse drug reaction: hospitalization	Indicates "Yes" if the adverse drug reaction required hospitalization or prolonged hospitalization	Category	Y	Yes

ADVERSE DRUG REACTION DESCRIPTION (listed one by one)					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
AESDISAB	Serious adverse drug reaction: permanent damage or significant disability	Indicates "Yes" if the adverse drug reaction was associated with a persistent or significant disability or incapacity	Category	Y	Yes
AESCONG	Serious adverse drug reaction: congenital anomaly or birth defect	Indicates "Yes" if the adverse drug reaction was associated with a congenital anomaly or birth defect	Category	Y	Yes
AENOTSER	Adverse drug reaction classified as not serious	Indicates whether the adverse drug reaction is determined to be "not serious"	Category	Y	Yes
AEACN1	Action taken with DTG	Action taken with DTG to manage the adverse drug reaction	Category	1	Dose adjustment
				2	Discontinue ARV drug
				3	Change regimen
				4	Other drug used to manage adverse drug reaction
				5	Dose adjustment and add other drug to manage adverse drug reaction
				6	Stop ARV drug and add other drug to manage adverse drug reaction
				7	Change regimen and add other drug to manage adverse drug reaction
				8	Other
				9	Unknown
AEACN1	Action taken – other	Indicates which other action was taken to manage the adverse drug reaction	Char		
DTCHREG	Date of changing regimen	Indicates the date on which the regimen was changed (DD-MMM-YYYY)	Date		
NEWREG	New regimen	Indicate which new regimen was given	Char		

ADVERSE DRUG REACTION DESCRIPTION (listed one by one)					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
6AEOUT	Outcome	Results after adverse drug reaction treatment. This refers to the outcome of the event in relation to the patient's status. • Select "not yet recovering" if the adverse drug reaction has not yet improved or recuperated. • Select "recovered without sequelae" if the patient fully recuperated without any sequelae • Select "recovered with sequelae" if the patient recuperated but retained pathological conditions resulting from the adverse drug reaction • Select "recovering" if the adverse drug reaction is improving but the patient has not yet fully recovered • Select "died due to adverse drug reaction" ("fatal, died due to adverse drug reaction") if the patient died as a result of the adverse drug reaction • Select "died, not due to adverse drug reaction" ("fatal, died not due to adverse drug reaction") if the patient died but the death was not directly due to the adverse drug reaction • Select "unknown" if the outcome was not known, not observed or not recorded	Category	1	Not yet recovering
				2	Recovered or resolved without sequelae
				3	Recovered or resolved with sequelae
				4	Recovering or resolving
				5	Fatal, died due to adverse drug reaction
				6	Fatal, died not due to adverse drug reaction
				9	Unknown
COVAL	Narrative or additional information	Additional comment	Char		
NULYN	Do you wish to mark this safety case as nullified?	This item should be used to indicate that a safety case previously recorded should be considered completely void (nullified), for example when the whole case was found to be erroneous	Category	N	No
				NA	Not applicable
				U	Unknown
				Y	Yes
NULREAS	Why are you nullifying the safety case?	Reason for nullification	Char		

Note: the adverse event section can be replicated as many times as needed to record all adverse drug reactions reported in the report..

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
IRIS	Immune reconstitution inflammatory syndrome	Indicates whether any opportunistic disease occurred after initiating DTG	Category	N	No
				U	Unknown
				Y	Yes
IRISTB	Immune reconstitution inflammatory syndrome – tuberculosis	Indicates whether tuberculosis developed as part of immune reconstitution inflammatory syndrome	Category	N	No
				U	Unknown
				Y	Yes
IRISTBDT	Immune reconstitution inflammatory syndrome – tuberculosis, date of diagnosis	Indicates the date of tuberculosis diagnosis if tuberculosis developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
IRISCRYP	immune reconstitution inflammatory syndrome – cryptococcal meningitis	Indicates whether cryptococcal meningitis developed as part of immune reconstitution inflammatory syndrome		N	No
				U	Unknown
				Y	Yes
IRISCRYPDT	immune reconstitution inflammatory syndrome – cryptococcal meningitis, date of diagnosis	Indicates the date of cryptococcal meningitis diagnosis if cryptococcal meningitis developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
IRISTOX	Immune reconstitution inflammatory syndrome – cerebral toxoplasmosis	Indicates whether cerebral toxoplasmosis developed as part of immune reconstitution inflammatory syndrome		N	No
				U	Unknown
				Y	Yes
IRISTOXDT	Immune reconstitution inflammatory syndrome – cerebral toxoplasmosis, date of diagnosis	Indicates the date of cerebral toxoplasmosis diagnosis if cerebral toxoplasmosis developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
IRISCMV	Immune reconstitution inflammatory syndrome – CMV retinitis	Indicates whether CMV retinitis developed as part of immune reconstitution inflammatory syndrome		N	No
				U	Unknown
				Y	Yes
IRISCMVDT	Immune reconstitution inflammatory syndrome – CMV retinitis, date of diagnosis	Indicates the date of CMV retinitis diagnosis if CMV retinitis developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
IRISKAP	Immune reconstitution inflammatory syndrome – Kaposi's sarcoma	Indicates whether Kaposi's sarcoma developed as part of immune reconstitution inflammatory syndrome		N	No
				U	Unknown
				Y	Yes
IRISKAPDT	Immune reconstitution inflammatory syndrome – Kaposi's sarcoma, date of diagnosis	Indicates the date of Kaposi's sarcoma diagnosis if Kaposi's sarcoma developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
IRISOTH1	Immune reconstitution inflammatory syndrome – other *(1)*	Indicates whether another condition was developed as part of immune reconstitution inflammatory syndrome *(1)*		N	No
				U	Unknown
				Y	Yes
IRISOTH1DT	Immune reconstitution inflammatory syndrome – other *(1)*, date of diagnosis	Indicates the date of diagnosis of the other condition (1) if CMV retinitis developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
IRISOTH2	Immune reconstitution inflammatory syndrome – other *(2)*	Indicates whether another condition was developed as part of immune reconstitution inflammatory syndrome *(2)*		N	No
				U	Unknown
				Y	Yes

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME					
Question code	**Question name**	**Additional information**	**Format**	**Category coding**	**Category labelling**
IRISOTH2DT	immune reconstitution inflammatory syndrome – other *(2)*, date of diagnosis	Indicates the date of diagnosis of the other condition (2) if CMV retinitis developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
IRISOTH3	Immune reconstitution inflammatory syndrome – other *(3)*	Indicates whether another condition was developed as part of immune reconstitution inflammatory syndrome *(3)*		N	No
				U	Unknown
				Y	Yes
IRISOTH3DT	Immune reconstitution inflammatory syndrome – other *(3)*, date of diagnosis	Indicates the date of diagnosis of the other condition *(3)* if CMV retinitis developed as part of immune reconstitution inflammatory syndrome (DD-MMM-YYYY)	Date		
MHTERM1	Comorbidities	Describe the relevant actual comorbidities	Char		
MHDECOD	Coding comorbidities	Dictionary-derived text description of MHTERM. Equivalent to the Preferred Term (PT in MedDRA)	Char		

Note: the medical history section can be replicated as many times as needed to record all adverse drug reactions reported in the report.

ANNEX 4.

WHO template for a chronic hepatitis B and C patient management card

Identification		
Unique identifier: ☐☐☐☐☐☐☐☐☐☐		
District:	Health unit:	District clinician or team:
Name:	First name:	Patient clinic number:
Sex: ☐Male ☐Female ☐Other	Date of birth (DD/MM/YYYY):__/__/____	Nationality:
Address:	District:	Telephone:

Infection status on enrolment	**Enrolment date:** __/__/____	
HBsAg: ☐Positive ☐Negative ☐Not done Date of first diagnosis of HBV infection: __/__/____	HBV DNA (IU/ml): value ☐Negative ☐Not done HDV RNA (IU/ml): ☐Positive ☐Negative ☐Not done	HBeAg: ☐Positive ☐Negative ☐Not done Anti HDV: ☐Positive ☐Negative ☐Not done
Anti-HCV: ☐Positive ☐Negative ☐Not done Date of first diagnosis of HCV infection: __/__/____	HCV RNA (IU/ml): value ☐Negative ☐Not done HCV genotype:	HCV core antigen: ☐Positive ☐Negative ☐Not done
Anti-HIV: ☐Positive ☐Negative ☐Not done	HIV treatment regimen:	Date HIV treatment started: __/__/____
Latest HIV viral load (copies/ml): ☐Not done	CD4 count (cells/mm^3): ☐Not done	
Tuberculosis: ☐Active ☐On treatment ☐No		
Injection drug use: ☐Active (last 12 months) ☐Past history ☐No	Daily alcohol consumption:	Metabolic syndrome:

Staging	**Staging date:** __/__/____	
ALT: IU/mL AST: IU/mL PLT: /mm^3	Clinical diagnosis of cirrhosis: ☐Yes ☐No	If yes, Child Pugh score:
APRI score: ☐Not done FIB4: ☐Not done	Transient elastography (kPa): ☐Not done	Liver biopsy stage (F): ☐Not done
Bilirubin: Total: µmol/l Direct: µmol/l	Ultrasound scan:	Prothrombin time / INR:

Hepatitis B treatment		
Past experience with treatment: ☐Yes ☐No	Past treatment regimen:	
HBV treatment regimen started (medicine):	Date started: __/__/____	Date stopped:__/__/___
First annual viral response assessment:		
Date tested: __/__/____	HBV DNA (IU/ml): ☐Positive ☐Negative ☐Not done	ALT: IU/mL

Hepatitis C treatment		
Past experience with treatment: ☐Yes ☐No	Past treatment:	
HCV treatment regimen started:	Date stated: __/__/____	Date completed: __/__/____
Sustained viral response assessment after treatment (usually at SVR12: 12 weeks after the treatment ends)		

Follow-up visits			
Unique identifier: ☐☐☐☐☐☐☐☐☐☐	Name:	First name:	Patient clinic number:

Date	Clinical assessment	Liver function test and staging					HBV tests			HCV tests	Renal function	Screening for hepatocellular carcinoma		Treatment regimen used	Side effects and toxicity	Observations
		ALT (IU/mL)	AST (IU/mL)	Platelets (number/ mL)	APRI	Transient elstrography (kPa)	HBsAg (±)	HBeAg (±)	HBV DNA (IU/mL)	HCV RNA (±)	Creatinine (mg/dl)	Ultrasound	AFP (ng/mL)			

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