Drug Safety

A comparison of active pharmacovigilance strategies used to monitor adverse events to antiviral agents: a systematic review

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Supplementary Material

Table S1. Description of the concepts used in the systematic review.

Concept	Description
Active pharmacovigilance	*"Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. (…) In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system",* by **ICH E2E Pharmacovigilance planning guideline**.
Adverse event	*"(…) any untowa rd medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product",* by **Good Pharmacovigilance Practices of the European Medicines Agency**.
Antiviral agent	*"(…) drugs approved by the Food and Drug Administration (FDA) for the treatment or control of viral infections. They target stages in the viral life cycle. An ideal antiviral agent should be effective against both actively replicating and latent viruses; however, most of the available antiviral agents are effective against only replicating viruses",* by **Encyclopedia of Microbiology**.

Table S2. Queries used for searching MEDLINE/PubMed, Web of Science and Scopus.

Search	MEDLINE/PubMed Search Strategy	Items found
	1st Concept - terms relating to active pharmacovigilance strategies	
#1	"Product Surveillance, Postmarketing"[mh] OR "Post-Marketing Product Surveillance"[tw] OR "Postmarketing Product Surveillance"[tw] OR "Product Surveillance"[tw] OR "Postmarketing Evaluation Stud*"[tw] OR "Drug Surveillance*"[tw] OR "Pharmacovigilance"[mh] OR "Pharmacovigilance*"[tw] OR "Active Pharmacovigilance"[tw] OR "Pharmacoepidemiology"[mh] OR "Pharmacoepidemiology"[tw] OR "Pharmaceutical Epidemiology"[tw] OR "Adverse Drug Reaction Reporting Systems"[mh] OR "Adverse Drug Reaction Reporting System*"[tw] OR "Drug Reporting System*"[tw] OR "Reporting System*"[tw] OR "Drug-Related Side Effects and Adverse Reactions"[mh] OR "Adverse Drug Reaction*"[tw] OR "Adverse Drug Event*"[tw] OR "Drug Side Effect*"[tw] OR "Side Effects of Drugs"[tw] OR "Drug Toxicit*"[tw] OR "Prescription Event Monitoring"[tw] OR "Prescription Monitoring*"[tw] OR "Prescription Drug Monitoring Program"[tw] OR (("Sentinel Surveillance"[mh] OR "Sentinel Surveillance"[tw] OR "sentinel initiative"[tw] OR "Mini-Sentinel"[tw] OR "Active Surveillance"[tw]) AND ("Drug-Related Side Effects and Adverse Reactions"[mh] OR "Adverse Drug Reaction*"[tw] OR "Adverse Drug Event*"[tw] OR "Drug Side Effect*"[tw] OR "Side Effects of Drugs"[tw] OR "Drug Toxicit*"[tw]))	
	2nd Concept – terms relating to antiviral agents	
#2	"Antiviral Agents" OR "Anti-Retroviral Agents" OR "Virus Inactivation" OR "Antiviral Agents" [Pharmacological Action] OR "Anti-infective Agent*"[tw] OR "Antiinfective Agent*"[tw] OR "Antiviral*"[tw] OR "Anti-retroviral*"[tw] OR "Antiretroviral*"[tw] OR "Virus Inactivation"[tw]	
	3rd Concept – terms relating to the outcome	
#3	Incidence[tw] OR prevalence[tw]	
#4	**#1 AND #2 AND #3**	**1087**

Search	Web of Science Search Strategy	Items found
	1st Concept - terms relating to active pharmacovigilance strategies	
#1	"Post-Marketing Product Surveillance" OR "Postmarketing Product Surveillance" OR "Product Surveillance" OR "Postmarketing Evaluation Stud*" OR "Drug Surveillance*" OR "Pharmacovigilance*" OR "Active Pharmacovigilance" OR "Pharmacoepidemiology" OR "Pharmaceutical Epidemiology" OR "Adverse Drug Reaction Reporting System*" OR "Drug Reporting System*" OR "Reporting System*" OR "Adverse Drug Reaction*" OR "Adverse Drug Event*" OR "Drug Side Effect*" OR "Side Effects of Drugs" OR "Drug Toxicit*" OR "Prescription Event Monitoring" OR "Prescription Monitoring*" OR "Prescription Drug Monitoring Program" OR (("Sentinel Surveillance" OR "sentinel initiative" OR "Mini-Sentinel" OR "Active Surveillance") AND ("Adverse Drug Reaction*" OR "Adverse Drug Event*" OR "Drug Side Effect*" OR "Side Effects of Drugs" OR "Drug Toxicit*")) (All Fields)	
	2nd Concept – terms relating to antiviral agents	
#2	"Anti-infective Agent*" OR "Antiinfective Agent*" OR "Antiviral*" OR "Anti-retroviral*" OR "Antiretroviral*" OR "Virus Inactivation" (All Fields)	
	3rd Concept – terms relating to the outcome	
#3	Incidence OR prevalence (All Fields)	
#4	**#1 AND #2 AND #3**	**473**

Search	Scopus Search Strategy	Items found
	1st Concept - terms relating to active pharmacovigilance strategies	
#1	TITLE-ABS-KEY ("Post-Marketing Product Surveillance" OR "Postmarketing Product Surveillance" OR "Product Surveillance" OR "Postmarketing Evaluation Stud*" OR "Drug Surveillance*" OR "Pharmacovigilance*" OR "Active Pharmacovigilance" OR "Pharmacoepidemiology" OR "Pharmaceutical Epidemiology" OR "Adverse Drug Reaction Reporting System*" OR "Drug Reporting System*" OR "Reporting System*" OR "Adverse Drug Reaction*" OR "Adverse Drug Event*" OR "Drug Side Effect*" OR "Side Effects of Drugs" OR "Drug Toxicit*" OR "Prescription Event Monitoring" OR "Prescription Monitoring*" OR "Prescription Drug Monitoring Program" OR (("Sentinel Surveillance" OR "sentinel initiative" OR "Mini-Sentinel" OR "Active Surveillance") AND ("Adverse Drug Reaction*" OR "Adverse Drug Event*" OR "Drug Side Effect*" OR "Side Effects of Drugs" OR "Drug Toxicit*")))	
	2nd Concept – terms relating to antiviral agents	
#2	TITLE-ABS-KEY ("Anti-infective Agent*" OR "Antiinfective Agent*" OR "Antiviral*" OR "Anti-retroviral*" OR "Antiretroviral*" OR "Virus Inactivation")	
	3rd Concept – terms relating to the outcome	
#3	TITLE-ABS-KEY (Incidence OR prevalence)	
#4	**#1 AND #2 AND #3**	**1871**

Table S3. Categorisation of reported clinical data sources used to obtain patient assessment information.

Label	Description
Laboratory tests	Deliberate solicitation and execution of specific laboratory tests as part of the study monitoring process, excluding those conducted within the standard patient care.
Physical examination	In-person physical evaluation conducted by a healthcare professional or researcher within the scope of the study.
Other Complementary Diagnostic and Therapeutic Procedures (CDTP)	Deliberate solicitation and execution of specific CDTP as part of the study monitoring process, excluding those conducted within the standard patient care.
Medical records	Extraction of data from patient's clinical records by a healthcare professional or researcher for monitoring purposes.
Patient's interview	Structured or unstructured interview or questionnaire administered to the patient, in-person or remotely, aimed at gathering reports of AE experienced by the patient up to that point.
Patient's self-report	Instructions provided to the patient by the researcher or healthcare professional to report the occurrence of any AE.
Healthcare professionals' interview	Structured or unstructured interview or questionnaire administered to the healthcare professional caring for the patient, in-person or remotely, aimed at gathering reports of AE experienced by the patient up to that point.
Caregiver's interview	Structured or unstructured interview or questionnaire administered to caregivers directly providing care to the patient, in-person or remotely, aimed at gathering reports of AE experienced by the patient up to that point.
Caregiver's self-report	Instructions provided to the caregiver by the researcher or healthcare professional to report the occurrence of any AE.

Table S4. Quality assessment of cohort studies using the Newcastle-Ottawa Scale, organized by clinical condition.

Study (Author, year)	Selection (0 to 4)				Comparability (0 to 2)	Outcome (0 to 3)			Total (0 to 9)	Quality score
	Representativeness of exposed cohort[1]	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of basis of design or analysis[2]	Assessment of outcome	Adequate follow-up length[3]	Adequacy of follow-up[4]		
HIV										
Khalili H et al. (2009)[1]	1	0	1	1	1	0	1	0	**5**	**Poor**
Modayil RR et al. (2010)[2]	1	0	1	1	1	1	1	1	**7**	**Good**
Nagpal M et al. (2010)[3]	1	0	1	1	0	0	1	1	**5**	**Poor**
Abaissa SG et al. (2012)[4]	1	0	1	1	1	1	1	1	**7**	**Good**
Bernal F et al. (2013)[5]	1	0	1	1	1	1	0	1	**6**	**Good**
Bezabhe WM et al. (2015)[6]	1	0	1	1	2	1	1	1	**8**	**Good**
Jha AK et al. (2015)[7]	0	0	1	1	0	0	1	1	**4**	**Poor**
Mann M et al. (2016)[8]	1	0	1	1	1	1	1	1	**7**	**Good**
Gudina EK et al. (2017)[9]	1	0	1	1	1	1	1	1	**7**	**Good**
Isa AM et al. (2018)[10]	1	0	1	1	1	1	1	1	**7**	**Good**
Oumar AA et al. (2019)[11]	1	0	1	1	0	1	1	1	**6**	**Poor**
Sarraf DP et al. (2020)[12]	1	0	1	1	0	1	0	1	**5**	**Poor**
Omolo BO et al. (2020)[13]	1	0	1	1	0	0	1	0	**4**	**Poor**
Ray S et al. (2023)[14]	1	0	1	1	1	1	1	1	**7**	**Good**
Bonfanti P et al. (2000)[15]	1	0	1	1	1	0	1	1	**6**	**Good**
Pujades-Rodríguez M et al. (2011)[16]	1	0	1	1	1	1	1	0	**6**	**Good**
Hongo H et al. (2021)[17]	1	0	1	1	1	1	1	1	**7**	**Good**
Ann H et al. (2019)[18]	1	0	1	1	2	0	1	1	**7**	**Good**

Tukei VJ et al. (2012)[19]	1	0	1	1	1	1	1	1	**7**	**Good**
Tetteh RA et al. (2015)[20]	1	0	1	0	1	1	1	0	**5**	**Fair**
Joseph AC et al. (2016)[21]	1	0	1	1	0	1	1	1	**6**	**Poor**
Jena A et al. (2009)[22]	1	0	1	1	1	1	1	1	**7**	**Good**
Sharma A et al. (2008)[23]	0	0	1	1	0	1	1	0	**4**	**Poor**
Influenza										
Komeda T et al. (2014)[24]	1	0	1	1	0	0	1	1	**5**	**Poor**
Komeda T et al. (2015)[25]	1	0	1	1	0	0	1	1	**5**	**Poor**
Komeda T et al. (2016)[26]	1	0	1	1	0	0	1	1	**5**	**Poor**
Kashiwagi S et al. (2012)[27]	1	0	1	1	1	0	0	1	**5**	**Poor**
Nakano T et al. (2021)[28]	1	0	1	1	1	0	0	1	**5**	**Poor**
Dalvi PS et al. (2011)[29]	1	0	1	1	1	0	0	1	**5**	**Poor**
Tahara T et al. (2013)[30]	1	1	1	1	2	0	1	1	**8**	**Good**
Nakazawa M et al. (2020)[31]	1	0	1	1	0	0	0	1	**4**	**Poor**
HCV										
Tinè F et al. (2010)[32]	1	0	1	1	1	1	1	1	**7**	**Good**
Suzuki F et al. (2018)[33]	1	0	1	1	0	1	1	1	**6**	**Poor**
Ahmed E et al. (2018)[34]	1	0	1	1	1	1	1	1	**7**	**Good**
Mizokami M et al. (2020)[35]	1	0	1	1	0	1	0	1	**5**	**Poor**
HBV										
Kim CW et al. (2018)[36]	1	0	1	1	1	1	1	1	**7**	**Good**

HIV: Human Immunodeficiency Virus; **HCV:** Hepatitis C Virus; **HBV:** Hepatitis B Virus

[1]The representativeness of the exposed cohort was deemed to be truly representative of the average population in the community with respect to relevant criteria (e.g., age, sex, diagnosis).

[2]The comparability of cohorts, based on the design or analysis, was considered with reference to whether they presented any sub-analysis or statistical adjustment for concomitant drugs or for medication adherence.

[3]The decision on whether the follow-up was long enough for outcomes to occur was based on the clinical judgement of the authors. Given the diverse range of antiviral agents used in our systematic review, establishing a consistent follow-up time is challenging. Therefore, we did not impose a specific cut-off for follow-up duration. Instead, we relied on the authors' clinical judgement, considering factors such as the individual's clinical condition, the specific antiviral agent or group of antivirals under study, and the study design, among other relevant considerations, to determine if the follow-up duration was sufficient for capturing the occurrence of adverse events.

[4]For the adequacy of follow-up of cohorts, we considered a proportion of 10% of missing outcome data as an acceptable threshold for assessing bias. This decision is based on the understanding that the occurrence of the outcome of interest is reasonably common in the context of adverse events associated with systemic antiviral medicines. While there is no consensus threshold described in the literature, with values typically ranging between 5% and 20%, our decision to adopt a 10% threshold is reinforced by the range of thresholds reported and the reasonably common nature of these events.

Quality score: *Good quality*: 3 or 4 points in the selection domain AND 1 or 2 points in the comparability domain AND 2 or 3 points in the outcome domain; *Fair quality*: 2 points in the selection domain AND 1 or 2 points in the comparability domain AND 2 or 3 points in the outcome/exposure domain; *Poor quality*: 0 or 1 point in the selection domain OR 0 points in the comparability domain OR 0 or 1 points in the outcome/exposure domain.

Table S5. Comprehensive overview of AE, severity and causality definitions, and active pharmacovigilance strategies employed in the included studies.

Study (Author, year)	AE, severity and causality definitions	Active FV strategy		
		Clinical data sources		
		Type of strategy	*Where the researcher/healthcare professional obtains the information for patient`s assessment*	Strategy description
HIV				
Khalili H et al. (2009)[1]	*ADR:* any noxious or unintended response to a drug, which occurs at doses normally used in human for the prophylaxis, diagnosis or treatment of disease or for the modification of physiological function according to WHO). *Severity:* based on AIDS Clinical Trials Group classifications, and Hartwig and Siegel. Causality: was evaluated using the Roussel Uclaf Causality Assessment Method (RUCAM) algorithm and WHO criteria for causality assessment.	Drug event monitoring	Patient's interview Laboratory tests	Follow-up visits were usually carried out at least monthly by experienced physicians and clinical pharmacist who could ascertain the occurrence of ADRs. Patients were also asked to report any ADRs upon occurrence. Complete and differential blood counts (CBC/diff) assessment was repeated at each visit or upon indication based on patients symptoms. Follow-up lipid profile, FBS, liver and renal function tests, serum lactate and CPK levels were measured at months 3, 6, and 12 of treatment and as indicated. LFTs were done at weeks 2, 4, 8, and 12 of treatment in patients on nevirapine-based regimens. At the onset of any adverse reaction (whether it caused ART discontinuation or not), a special ADR form was filled containing the following data: description of the reaction, severity of the reaction, any necessary intervention, outcome, and causal relationship between drugs and reaction.
Modayil RR et al. (2010)[2]	*Severity:* based on modified Hartwig and Siegel scale. *Causality:* based on WHO ADR probability scale and Naranjo's algorithm.	Drug event monitoring	Medical records Patient's interview	Patients were intensively monitored for any ADRs during follow-up visits to the ART centre. ADRs were identified by an interview with the patient and/or their attendants, as well as a review of out-patient case records, laboratory reports, clinician's notes and prescriptions at each follow-up visit.

Nagpal M et al. (2010)[3]	*ADR:* based on WHO criteria. Causality: *ADR:* based on WHO probability scale.	Drug event monitoring	Medical records Patient's interview	From the patients file, record was made of the findings of complete general physical, systemic examination and all laboratory investigations. ADR monitoring was done in a systematic manner adopting both spontaneous and intensive monitoring approaches. Patients were asked in detail about the duration of AE, its severity and any concomitant medication taken. At the same time, the patients were asked about common ADRs as mentioned in the literature. A diary card was also given to each patient for recording the adverse events which was checked at every visit.
Abaissa SG et al. (2012)[4]	*AE:* based on the Ministry of Health Guidelines for use of antiretroviral drugs in Ethiopia, Addis Ababa, 2008, and the AIDS Clinical Trial Group (ACTG) toxicity grading system. *Severity:* classified as grade III and IV according to AIDS Clinical Trials Group classifications.	Drug event monitoring	Patient's interview Laboratory tests	Patients were recruited from the HIV outpatient clinics. Data were collected by trained physicians using a structured questionnaire, which included sociodemographic information, and clinical and laboratory findings. The patients were prospectively followed at baseline, 2 weeks, 4 weeks, 8 weeks, 12 weeks and 18 weeks after ART initiation, or as required when patients developed serious AE. Clinical evaluation was performed at entry and at each subsequent visit. Haematological and biochemical tests were performed at baseline/entry (just prior to ART commencement), at 4 weekly scheduled visits after the patient was started on ART and when clinically indicated.
Bernal F et al. (2013)[5]	*AE:* Chile Ministry of Health in its HIV/AIDS clinical guide, 2009.	Drug event monitoring	Patient's interview Laboratory tests	The program consists of a weekly control during the first month of treatment. During each visit, ADR were registered and notified to the National Center for Information on Medicines and Pharmacovigilance (CENIMEF). For the detection of laboratory alterations, metabolic tests were requested, prior to medical control.
Bezabhe WM et al. (2015)[6]	*ADR:* WHO definition. *Severity AE:* based on the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.	Drug event monitoring	Patients' self-report Healthcare professionals' interview Caregivers' interview Patients' interview Medical records	A research pharmacist was assigned to each hospital's ART clinic to assess ADRs throughout the study period. Patients were also asked to report any potential ADRs. ADRs that continued for subsequent appointments without recovery were reported once. The research pharmacists interviewed patients, caregivers and physicians, reviewed patients' medical records and documented detailed information for each of the potential ADRs that patients experienced.
Jha AK et al. (2015)[7]	NR	Drug event monitoring	Patient's interview	After initiation of the therapy, the patients were examined for any AE that occurred, its type and severity, or any ther abnormal laboratory finding. These subjects were followed up for a period of two months. At each follow-up visit, the adverse clinical events and the abnormal laboratory findings were documented. The case sheets of the included subjects were studied and the information obtained was entered into the Suspected Adverse Event

				Reporting Form. The subjects were not interviewed by the investigator. When any other information was required, the treating physician was contacted. Any AE observed by the investigator or treating physician was noted in the form and any untoward event was labeled as an AE only after the concurrence of treating physician.
Mann M et al. (2016)[8]	NR	Sentinel sites	Medical records Patient's interview	The presence or absence of AEs as well as demographic and clinical information was recorded onto a novel and pre-tested active surveillance data collection form. Other clinical care information at ART sites is routinely recorded in paper medical records. The medical records have been shown to have high quality information on therapy, clinical progress notes, and laboratory values. Part A of the form was completed for all study eligible patients at the initial visit. During each follow-up visit the physician actively recorded the presence or absence and type of any AEs on part B of form. A list of common AEs such as abdominal pain, anemia, serious skin reaction, and others was printed at the bottom of Part B of the form, and the physician recorded presence/absence for these events based on his/her opinion. The active surveillance data collection form stayed with the medical record throughout the pharmacovigilance activity.
Gudina EK et al. (2017)[9]	*ADR:* based on WHO criteria; only clinical conditions known to arise from potential agent, in the absence of other compelling medical conditions, were attributable to ADR. *Severity:* based on grade III and IV according to WHO criteria.	Drug event monitoring	Medical records Laboratory tests Patient's interview	Baseline data collected from participants included socio-demographic profile, general medical conditions, laboratory parameters and components of HIV care given to them (ART regimen, treatment for OI and prophylaxis given). Participants were subsequently followed from baseline for occurrence of ADR related to ART using clinical parameters and laboratory data where applicable. A particular emphasis was given to the first 6 months after ART initiation as most of the toxicities tend to occur during this time. These data were obtained from medical records for patients who were started on ART before 2009 (before recruitment started). Patients were assessed on each visit using checklists prepared for routine follow-up evaluation. In patients with suspected ADR, all necessary laboratory tests were done as needed.
Isa AM et al. (2018)[10]	*AE:* All events that occurred during this period. *ADR:* based on WHO criteria.	Drug event monitoring	Medical records Patient's interview	ADR monitoring was carried out using spontaneous reporting by patients and by active surveillance in the form of targeted spontaneous reporting by the primary investigator in conjunction with the ART clinician, ART focal pharmacist and the adherence counsellor. Data were collected using patient interviews (conducted between 8:00 am and 2:00 pm during clinic days), medical records and follow-up. Other relevant information, such as

	Severity: based on Hartwig severity assessment scale.			current ART regimen and patient medical and medication history were extracted from the patients' medical folder. Patients were asked to describe any ADRs they experienced from their ART, and whether the ADRs they experienced had made them skip or stop taking their medications. Data were collected using the data collection form, which had been developed from a survey of literature and pilot tested before commencement of the study. Follow-up was carried out for a period of 6 months, with an interval of 1 month for new patients and 2 months for patients on refill appointment.
Oumar AA et al. (2019)[11]	*Causality:* based on Naranjo's algorithm.	Drug event monitoring	Medical records Patient's interview	Each patient was interviewed and their medical charts were reviewed at each follow-up visit for any signs of ADR. A senior clinical pharmacist assessed and discussed any suspected or documented ADR with the physicians' team.
Sarraf DP et al. (2020)[12]	*ADR:* defined as any response to a medicine which is noxious and unintended, and which occurs at doses normally used in patients.	Drug event monitoring	Medical records Patient's interview Physical examination	A semi-structured proforma was prepared using the relevant literatures to collect the data. The patient were followed up on monthly basis when they visited the ART clinic for refilling of the prescription. Face-to-face interview was carried out using the questionnaire and general physical and systemic examinations were performed to identify ADRs. Hospital records and laboratory reports, clinician's notes and prescriptions were also reviewed for relevant data.
Omolo BO et al. (2020)[13]	*AE:* based on WHO ART guidelines.	Drug event monitoring	Patients' interview	Data were recorded during each patient's monthly visit, and included demographic characteristics (sex, race, and age), pain information, TB status, drug regimen and clinical evaluation variables. Also, information on the adverse events and complications of HIV and ART at each study visit was recorded.
Ray S et al. (2023)[14]	*ADR:* defined as any response (clinical/ laboratory) to a medicine which is noxious and unintended, and which occurs at doses normally used in man. *Causality:* based on WHO ADR probability scale and Naranjo's algorithm. *Severity:* based on modified Hartwig and Siegel scale.	Drug event monitoring	Patient's interview Patients' self-report	During the first 6 months after ART initiation, occurrence of any new event in the patients was actively enquired during each visit and evaluated for possible ADR. In addition, patients were encouraged to make a telephonic call or return to the center in case of development of any new symptom even when the scheduled visit was not due.

Bonfanti P et al. (2000)[15]	*AE:* any response to the combination therapy that is either harmful or unwanted and that results from normal therapeutic dosage; lack of therapeutic success is excluded from this definition, as re poisoning (whether intentional or accidental) and overdose). *Severity:* based on the NIH, NIAID, DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. *Causality:* based on Roussel Uclaf Causality Assessment Method (RUCAM) algorithm.	Drug event monitoring	Patient's interview Patients' self-report Laboratory tests	Follow-up visits are carried out by each individual center at varying times, but at least every 2 months, by experienced physicians who an readily ascertain the occurrence of AE. Blood tests are performed during such visits. Patients are also asked to report any serious AE when they occur. At the onset of any AE (whether it causes treatment discontinuation or not), a special card is filled containing the following data: description of the reaction, seriousness of the reaction, outcome, concomitant treatment, and causal relationship between drugs and reaction).
Pujades-Rodríguez M et al. (2011)[16]	*Severity:* based on grading scale from the Division of AIDS, National Institute of Allergy and Infectious Diseases, version 1.0 December 2004.	Registry	Patient's interview	At each consultation or hospitalization individual patient data were prospectively collected using standardized forms and entered into FUCHIA.
Hongo H et al. (2021)[17]	*ADR:* as AE suspected to be related to DTG evaluated by the reporting physician and the sponsor. *Severity:* evaluated by the sponsor.	Drug event monitoring	Patient's interview	A standardized survey form was used to collect demographic, safety, and effectiveness domestic data. Specific AE as well as their dates of onset, clinical course, treatment, seriousness, outcome, causal relationship to disease or drugs, and presence or absence of abnormal changes in laboratory values (if measured) were collected.
Ann H et al. (2019)[18]	*AE, ADR and severity:* based on WHO-ART 092 (Korea Institute of Drug Safety & Risk Management).	Drug event monitoring	Patient's interview	Each physician decided patient visit schedules based on their routine practices. At the initial visit, demographic information, medical history, concomitant medications, laboratory values including viral load, CD4+ cell counts (if any) were recorded. Because of the non-interventional design of the study, not all the subjects had their HIV-1 RNA viral load and CD4+ T cell counts every visit. Any results of HIV RNA viral load and CD4+T cell counts as a part of standard of care within the study period were collected for analysis. Physicians were guided to record any treatment-emergent AE during the follow up visits.

Tukei VJ et al. (2012)[19]	*AE/ADR:* defined as a physician-documented occurrence or worsening of any undesirable symptom or sign (including an abnormal laboratory finding) temporally associated with the use of ARV drugs. *Severity:* based on US National Institute of Allergy and Infectious Diseases Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (grading table) Version 1.0.	Drug event monitoring	Patient's interview Laboratory tests	At every visit, clinical information on probable or confirmed adverse events was recorded in the patient's chart and appropriate laboratory investigations were carried out. Patients starting ART were scheduled to return to the clinic 2, 4, and 8 weeks after starting ART. Thereafter, routine monthly follow-up at the clinic involved drug refills, assessment for adverse events, and assessment of adherence to medication. In addition, patients were encouraged to return to the clinic any time they developed symptoms of disease or probable drug toxicity. At each visit, a structured questionnaire designed to capture possible adverse events was filled by the physicians.
Tetteh RA et al. (2015)[20]	NR	Drug event monitoring	Patient's interview Healthcare professionals' interview	Active follow-up for adverse events and adherence to prophylaxis schedule were performed by trained research assistants through telephone contact on days 3 and 10 after drug dispensing for those on the 3-day schedule and on days 3, 10, 20, 28 and 35 after drug dispensing for those on the 28 days schedule. In addition to the active follow-up, exposed HCWs/HCSs were asked to report events of medical concern (literally "anything that worries you") at any time during the follow-up period, noting especially the following signs; fever, rash, lymphadenopathy, dark-coloured urine, sore throat and bruising or bleeding from any part of the body. A structured questionnaire, interview guide was used to collect data from exposed HCWs/HCSs. Event data on adverse events was first recorded according to how the patient described the event (verbatim) and then reviewed qualitatively and coded using the MedDRA.
Joseph AC et al. (2016)[21]	*Severity*: based on modified Hartwig and Seigel criteria. *Causality:* based on WHO causality scale and Naranjo s algorithm.	Drug event monitoring	Patient's interview Physical examination Laboratory tests Other CDTP	Information regarding patients were obtained using a structured proforma. Physical findings and the investigations including complete blood count, liver function test, renal function test, random blood sugar, lipid profile, urine routine examination, serum calcium and phosphate estimation were recorded before starting the treatment and at 4 months, 8 months and 12 months. Ultrasonogram of abdomen was done at the initiation of treatment 6 and 12 months and in case of any specific reason/need in between. The patients were followed up at 2 months interval for clinical examination and the details of adverse events, if any occurred during this period were also recorded in the proforma. The data regarding the presence and absence of subjective side effects were obtained by asking leading questions to the patients or the accompanying person.

Jena A et al. (2009)[22]	NR	Drug event monitoring	Physical examination Laboratory tests Other CDTP Patient's interview	A detailed medical history was obtained and general physical examination was performed. Baseline investigations in the form of hemogram, liver function test (LFT), renal function test, lipidogram, electrocardiogram (ECG), and chest x-ray were obtained. The study group was followed up prospectively for 6 months. At 2, 6, 14, and 24 weeks, a questionnaire containing adverse effects of ARV medications was recorded. The occurrence of new symptoms was noted and relations to drugs were analyzed.
Sharma A et al. (2008)[23]	NR	Drug event monitoring	Patient's self-report Physical examination	All patients were asked to visit the clinic if they developed any symptoms or on a monthly basis. They were screened clinically and investigated suitably for any ADRs.
Influenza				
Komeda T et al. (2014)[24]	*AE:* defined all untoward or unintended signs (including abnormal laboratory test results), symptoms, or diseases occurring following peramivir administration, regardless of the causality. *ADR:* defined as AE whose causality to peramivir could not be ruled out, i.e., those other than "unrelated," as determined by the participating physicians or sponsor.	Drug event monitoring	Patient's interview	This study was implemented in a continuous investigation system, wherein the participating physicians were instructed to continuously complete survey forms. They provided a peramivir safety and effectiveness check sheet to patients under treatment and requested to complete it. The participating patients completed the check sheet with regard to details such as time course of symptoms and daily maximum body temperature, and returned the sheet at the next hospital visit or posted it to the physician. The physicians completed the survey forms, including the items related to AE, by referring to the check sheets for all patients promptly after completing the observation period, including for those who did not provide adequate safety information because of failure to revisit after the first time or to submit the check sheet.
Komeda T et al. (2015)[25]	*AE:* defined as all untoward or unintended signs (including abnormal laboratory test results), symptoms, or diseases occurring following peramivir administration, regardless of the causality.	Drug event monitoring	Patient's interview Caregiver's interview	This study was implemented in a continuous investigation system, wherein the participating physicians were instructed to continuously complete survey forms. They provided a peramivir safety and effectiveness check sheet to patients or their guardians under treatment and requested to complete it. The participating patients completed the check sheet with regard to details such as time course of symptoms and daily maximum body temperature, and returned the sheet at the next hospital visit or posted it to the physician. The physicians completed the survey forms, including the items related to AE,

	ADR: defined as AE whose causality to peramivir could not be ruled out, i.e., those other than "unrelated," as determined by the participating physicians or sponsor.			by referring to the check sheets for all patients promptly after completing the observation period, including for those who did not provide adequate safety information because of failure to revisit after the first time or to submit the check sheet.
Komeda T et al. (2016)[26]	*AE:* defined as all untoward or unintended signs (including abnormal laboratory test results), symptoms, or diseases occurring following peramivir administration, regardless of the causality. *ADR:* defined as AE whose causality to peramivir could not be ruled out, i.e., those other than "unrelated," as determined by the participating physicians or sponsor.	Drug event monitoring	Patient's interview	This study was implemented in a continuous investigation system, wherein the participating physicians were instructed to continuously complete survey forms. The physicians completed the survey forms, including baseline characteristics of the inpatients and the items related to AE. The physicians completed the survey forms, including baseline characteristics of the patients and the items related to adverse events (AEs) and effectiveness.
Kashiwagi S et al. (2012)[27]	*AE:* medically untoward events emerging following administration of laninamivir. *Causality:* AE that were clearly or likely to be causally related to the study drug were defined as ADR.	Drug event monitoring	Patient's self-report Patient's interview	The participating physician asked each relevant patient to perform the following study activities to evaluate the safety of laninamivir: contact the participating physician to give details if any unfavourable symptom occurred within 15 days of inhalation of laninamivir; in the event of unfavourable symptoms, document the AE in a patient diary, including the date and time of onset, condition of the patient at onset (while sleeping, just after awakening, while awake), duration of the symptoms, body temperature at the onset of symptoms, and whether an antipyretic was used within 4 h before the onset of symptoms. Then either send the patient diary by mail or bring it in person to the attending physician.
Nakano T et al. (2021)[28]	*AE:* medically untoward events emerging following administration of laninamivir. *ADR:* that were clearly or likely to be causally related to the study drug.	Drug event monitoring	Caregiver's self-report	Investigators asked the legal representative of a subject to record any unfavorable symptoms newly develop within 15 days of inhalation of the study drug.

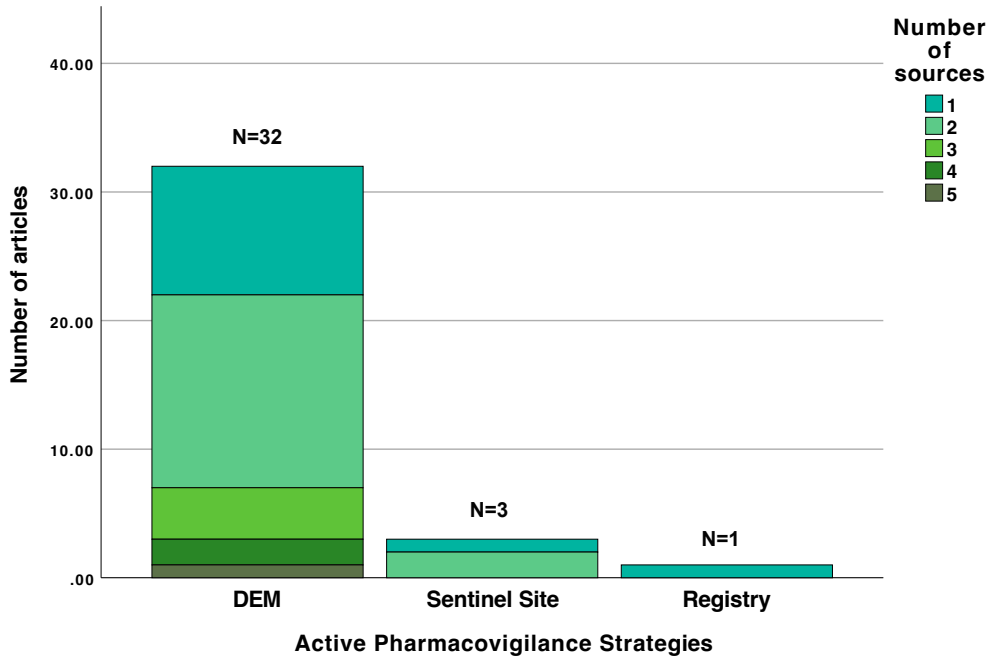
Dalvi PS et al. (2011)[29]	*Severity:* based on modified Hartwig and Seigel criteria.	Drug event monitoring	Caregiver's interview Caregiver's self-report	The children were followed up for adverse events for a period of 10 days after receiving first dose of oseltamivir. The parents or guardians of children were asked to note development of new symptoms or worsening of existing symptoms in children and to report it to the hospital if necessary, during the study period. Monitoring for adverse events to oseltamivir was done by direct questioning for symptoms and clinical examination on day 5 and day 10. Assessment of neurological adverse events included questions to parents or guardians and children (>5 years). Parents were also encouraged to report such symptoms developed after the study period and within 30 days of receiving first dose of oseltamivir.
Tahara T et al. (2013)[30]	The child's pediatrician was then to decide whether each symptom was an AE or ADR on the basis of details in the returned "Symptom Observation Form".	Drug event monitoring	Physical examination Caregiver's self-report	Gender, age, body weight, vaccination status, body temperature, virus type (result of antigen detection kit test), and date and time of fever or symptom onset were recorded at the first clinic or hospital visit. During the first week, guardians or family members were to record their child's body temperature every morning and evening, the severity of influenza symptoms such as nasal symptoms and cough, and any other symptoms of concern. Thereafter, they were to record body temperature once a week and any symptoms of concern. The child's pediatrician was then to decide whether each symptom was an AE or ADR on the basis of details in the returned "Symptom Observation Form", and to enter the relevant data in the patient's case report form. If a "Symptom Observation Form" was not returned, the pediatrician checked for occurrences of AEs by contacting the child's guardian or family member by telephone.
Nakazawa M et al. (2020)[31]	*ADR:* defined as AE whose causality to baloxavir could not be ruled out (i.e., other than "unrelated"), as determined by the physician or sponsor.	Drug event monitoring	Patient's self-report	Treating physicians provided a questionnaire to enrolled patients on the day of baloxavir treatment. Patients completed the questionnaire and returned it to the treating physician by mail. Treating physicians filled out the study forms on the basis of patient answers. AEs were collected using the patient questionnaire. Physicians then reported the name of the AE, date of onset, outcome (recovered, recovering, not recovered, recovered but with sequelae, death due to an AE, unknown), date of outcome, seriousness (serious, non-serious), and causal relationship to baloxavir.
HBC				
Tinè F et al. (2010)[32]	*Severity:* graded by the investigators as mild, moderate, severe or lifethreatening, based on modified WHO grading system.	Drug event monitoring	Patient's interview	Data collected included adverse event description, onset date, duration, intensity, relationship to study drugs and required treatment (if any). Data were registered at each visit during follow-up, together with the physician's decision on any modification to the dose schedule in order to continue or immediately discontinue therapy.

				On-treatment visits were performed at discrete times, that is at 15, 30, 60, 90 days from start, and then every 30 days up to the end of scheduled treatment. After the end of treatment, a visit was performed at 90 days and the final visit at 180 days.
Suzuki F et al. (2018)[33]	*ADR:* all AE other than those that were ‘‘not related’’ to drugs under study.	Sentinel sites	Patient's interview	Assessment data of postmarketing surveillance participants were obtained from case report forms (CRFs) at the participating sites.
Ahmed E et al. (2018)[34]	*AE and severity:* based on FDA regulation.	Drug event monitoring	Patient's interview Patients self-report Laboratory tests	Data was collected by the researchers using a structured interview questionnaire. Patients receiving DAAs were evaluated for AE every month through a detailed interview on the basis of preformed questionnaire. Follow up laboratory tests were done every month throughout the treatment period and at the end of treatment All patients were invited to report any changes in their health status or wellbeing during the treatment period.
Mizokami M et al. (2020)[35]	NR	Sentinel sites	Medical records Patient's interview	Data were collected using standardized electronic case report forms (eCRFs) from patients’ medical records at the clinical sites on demographics, medical history, prescribed medications, laboratory measures and treatment-emergent AEs. All treatment-emergent AEs were identified by treating physicians during routine clinical practice and reported using the standardized eCRFs, which collected detailed descriptions of the AEs, including seriousness and assessment of causal relationship to treatment.
HBV				
Kim CW et al. (2018)[36]	*AE:* based on 2010 WHO Adverse Reaction Terminology criteria.	Drug event monitoring	Patient's self-report	Investigators recorded the patient demographics, disease information, drug administration reports, patient-reported AEs, and clinical laboratory.

NR: Not Reported; **HIV:** Human Immunodeficiency Virus; **HCV:** Hepatitis C Virus; **HBV:** Hepatitis B Virus

Figure S1. Global traffic-light plot for risk of bias based on NOS scale.

Figure S2. Stacked bar chart of the number of articles by active pharmacovigilance strategy based on the number of clinical data sources used.



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