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Pharmacovigilance for antiretroviral drugs in Africa, lessons from a study in Abidjan, Cote d'Ivoire:

Pharmacovigilance for antiretroviral drugs in Africa

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Abstract

Background—While antiretroviral treatment (ART)-related adverse drug reactions (ADR) are documented in industrialized countries, there is no pre-existing surveillance system dedicated to ADR monitoring in most African countries. We assessed knowledge towards pharmacovigilance among ART prescribers and available capacity of HIV clinics to conduct ADR monitoring in Abidjan, Côte d'Ivoire.

Methods—A questionnaire was administered to ART prescribers, to assess their knowledge towards the occurrence of ADRs. A retrospective ADR survey was also conducted, based on a data query of treatment modification/interruptions in three HIV clinics. Clinical monitors went back to medical charts to review and validate the reasons of the treatment modification/interruptions.

Results—Of the 81 ART prescribers interviewed, 25 (31%) declared not grading ADRs and 12 (14.8%) declared notifying ADRs to the national regulatory authorities. Among 5,252 adult ART-treated patients who attended the participating clinics in 2008, 599 treatment modifications were identified. Reasons for treatment modification/interruptions identified in the electronic database were documented in the medical charts in 554 (92.5%) cases, ADR accounting for 273 (45.5%) cases. Toxicity related to ART was graded in only 58 (21%) cases in the medical charts.

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Discussion—This study describes challenges limiting the implementation of reliable pharmacovigilance activities in HIV clinics in Côte d'Ivoire. The lack of knowledge of ART prescribers concerning ADR grading does not support the spontaneous reporting of ADRs. Using treatment modification/interruptions for ADR monitoring appears feasible but improvements are needed to respond to key questions related to drug toxicities in the context of ART scale up in Africa.

Keywords

pharmacovigilance; HIV/AIDS; antiretroviral; sub-Saharan Africa

Introduction

Since 2002, access to antiretroviral treatment (ART) has dramatically improved with now three million of HIV-infected patients accessing ART in sub-Saharan Africa [1]. In Côte d'Ivoire, since 2008 ART has been free of charge. In January 2009 a total of 57,833 patients living with HIV/AIDS followed-up at 274 HIV centres received ART [2]. The combination of two nucleoside and one non-nucleoside reverse transcriptase inhibitors was prescribed in 83% of those initiating ART, the most frequently prescribed was the fixed-dose combination of stavudine/lamivudine/nevirapine (Triomune®) in 49% of cases. In case of therapeutic failure the second-line treatment mainly relied on protease inhibitors such as indinavir or lopinavir boosted with ritonavir [3]. While ART-related adverse drug reactions (ADR) have been reasonably well documented in industrialized countries with pre and post-marketing studies, there is no pre-existing surveillance system dedicated to ADR monitoring in most African countries. Information related to ART toxicity in these resource-limited settings has been provided so far from clinical trials and observational studies of limited sample size. Drug-related toxicity is now the most common cause of treatment interruption or modification in ART-treated patients in sub-Saharan Africa [4, 5]. Moreover, access to ART in sub-Saharan Africa occurs in a different context compared to industrialized countries in terms of target populations (i.e. a majority of women, frequent pregnancies, large number of children), access to care (i.e. limited resources for diagnosis of side effects, use of more toxic ART and predominant use of generic drugs) and co-morbidities (hepatitis, tuberculosis, malaria) [1].

In industrialized countries, health care providers are encouraged to declare severe or unknown drug-related adverse events, to a local pharmacovigilance (PV) center. From the network of PV centers, a national database is maintained and information on drug characteristics and safety regularly updated [6]. In Côte d'Ivoire, West Africa, PV activities are under the responsibility of the Directorate of Pharmacy and Medicine (DPM), a section of the Ministry of Health. Infrastructure and human resources necessary for the development of PV exist but their operations are limited by a lack of a legal framework, adverse event reporting remaining voluntary without mandatory obligation.

So far, PV activities in African countries have mainly focused on malaria medications [7–9]. Enlarging PV activities to ART drugs entails a particular need to assess the capacity to conduct ADR monitoring in HIV-infected patients. We assessed the knowledge of ART prescribers towards PV activities as well as available resources dedicated to ADR monitoring in a network of HIV clinics in West Africa.

Methods

Design and setting

This study was conducted in two steps. First, a cross-sectional survey was conducted among ART prescribers currently delivering ART in the urban area of Abidjan. We selected a convenience sample of HIV clinics delivering ART at different levels of care (referral hospitals, public/private medical centers and non governmental organizations). All wards currently following HIV-infected patients in the three referral hospitals of Abidjan as well as a subset of public/private medical centers and non governmental organizations located near these referral hospitals were solicited to participate. The HIV clinics that agreed to participate in the present study were sequentially investigated. A clinical monitor was in charge to administer a questionnaire focusing on ADR management and PV knowledge to all ART prescribers currently delivering ART in the selected HIV clinics.

The second part of the study aimed to document available information on ADR monitoring in cohorts of HIV patients receiving ART and followed in HIV clinics participating to the International epidemiological Database to Evaluate AIDS (IeDEA) West Africa collaboration [10]. By collecting and harmonizing data from multiple HIV/AIDS cohorts from industrialized and resource-limited countries, the IeDEA international network aims to address unique and evolving research questions in the field of HIV/AIDS care and treatment. In the West African region, this collaboration was initiated in July 2006 and as of May 2010 involved 15 adult HIV clinics spread over seven countries (<http://www.iedeawestafrika.org>). For logistic constraints, only three of the five HIV clinics participating to the IeDEA West Africa collaboration in Côte d'Ivoire, were randomly sampled to participate. A retrospective collection of ADRs was conducted, based on a data query of treatment modification/interruptions registered from January 1st, 2008 to December 31st, 2008 using the computerized IeDEA West Africa database. For validation purpose, extracted data on treatment modification/interruptions were matched with the respective pharmacy database currently delivering ART in the selected HIV clinics. As the reasons for modification/interruptions of ART were not routinely reported electronically in the database, clinical monitors went back to medical charts, reviewed and validated the reasons of the treatment modification/interruptions and filled in dedicated standardized case report forms.

Statistical analysis

We compared knowledge of ART prescribers according to their workplace (referral hospital wards vs other wards) using Pearson's χ^2 , Fisher's exact test or Wilcoxon test when appropriate. Incidence of ADRs were estimated by dividing the number of events by the total number of patients at risk in 2008 and reported per 100 person-years of follow-up (/100 PY) with their respective 95% confidence intervals (95% CI). All statistical analyses were performed using Epi Info software, version 6 (US Centers for Disease Control and Prevention, Atlanta, GA, USA).

Results

Knowledge towards pharmacovigilance

Of the 84 HIV clinics listed as currently delivering ART in the urban area of Abidjan, 21 were selected and agreed to participate. A single clinical monitor administered the questionnaire to all the 81 ART prescribers from these participating HIV clinics in March 2009. Among them, 48 (59.2%) were from referral hospital wards, 17 (21%) from public or private district medical centers and 16 (19.8%) from non governmental organizations. All ART prescribers were medical doctors (they are the only health professionals allowed to prescribe ARV drugs in Côte d'Ivoire). Overall, 25 of the respondents (30.6%) declared not

staging ADRs, 23 (28.3%) knew the existence of the local PV center and 12 (14.8%) declared notifying ADRs to the national regulatory authorities. An internationally validated grading system to assess the severity of ART toxicity was used by 37 (77.1%) of 48 ART prescribers from the referral hospital wards versus 19 (57.6%) of 33 ART prescribers from other wards ($p=0.06$). The knowledge of the national PV center and the proportion of ART prescribers who notified ADR were not significantly higher in the referral hospital wards compared to other wards (Table 1).

Adverse drug reaction monitoring

In 2008 5,252 HIV-infected patients made at least one visit in the three participating HIV clinics. Their median time spent on ART at that time was 25.8 months (inter quartile range [IQR] 12.8–40.8). Of these, 498 (9.5%) patients experienced at least one treatment modification/interruption for a total of 599 modification/interruptions events reported. The most frequently reported reason was ADR which accounted for 273 (45.5%) treatment modification/interruptions in 244 patients, yielding an incidence rate of 5.2 (95% CI 4.6–5.8) ADRs/100 PY. The incidence of ADRs in patients on ART for <1 year was 12.5 (95% CI 10.6–14.3)/100 PY versus 2.9 (95% CI 2.4–3.5)/100 PY in patients on ART for ≥ 1 year. The patients who experienced an ADR had a median age of 39 years (IQR 34–46), a sex ratio (male:female) of 0.33:1 and a median CD4 count at ART initiation of 154 (IQR 56–239) cells/mm³. The other reasons for treatment modification/interruptions were treatment failure in 91 (15.2%), pregnancy or planned pregnancy in 90 (15.1%), tuberculosis in 31 (5.2%) and other reasons (i.e. stock-out, voluntary treatment interruption) in 69 cases (11.5%). Reasons for treatment modification/interruptions identified in the electronic database were not documented in the medical charts in 45 patients (9.0%). The distribution of ADRs according to the ARV drugs that were withdrawn is summarized in table 2.

Peripheral neuropathy accounted for 123 (45.9%) of the 268 ADR-related treatment modifications for which the ART drugs withdrawn were specified in the medical charts. Stavudine was the most frequently withdrawn drug, stavudine alone, accounting for 124 (46.3%) of the documented ADR-related treatment modifications. The distribution of ADRs varied according to ART exposure. Of the 155 ADRs reported in patients on ART for <1 year, the four most frequent were peripheral neuropathy in 63 (40.6%), cutaneous reaction in 38 (24.5%), haematological disorders in 15 (9.7%) and gastrointestinal disorders in 10 (6.4%) cases. Of the 118 ADRs reported in patients on ART for ≥ 1 year, the four most frequent were peripheral neuropathy in 60 (51%), lipodystrophy in 19 (16.1%), central nervous system disorders in 10 (8.5%) and cutaneous reaction in 6 (5.1%) cases.

When retrospectively reviewing the available information related to ADRs, the toxicity grade was specified in the charts in only 58 (21.2%) of the 273 ADRs. For clinically assessed toxicity, the grade was specified in 28 (22.4%) of the 123 cases of peripheral neuropathy, 10 (21.7%) of the 46 cutaneous reactions and five (25%) of the 20 cases of lipodystrophy. For toxicity that required biological investigations, the grade was specified in one (5%) of the 20 hematological disorders and in none of the 10 cases of hepatic toxicity.

Discussion

This pilot survey describes for the first time patterns of knowledge of ART prescribers in Abidjan, Côte d'Ivoire. We also describe the monitoring features of ADRs related to ART using a retrospective surveillance method.

Knowledge towards pharmacovigilance

This study highlighted the lack of information of ART prescribers concerning ADR staging and reporting to the appropriate regulatory authorities. Only one-third of ART prescribers knew the existence of a national PV center in Côte d'Ivoire which is consistent with previous reports from Nigeria where 40.4% of the 120 medical doctors interviewed in the Lagos State University Teaching Hospital knew the existence of a national PV center [11]. Moreover, we documented an important heterogeneity of the practices related to the use of grading systems to assess ADR severity. There are currently several grading systems for adverse events that have been developed for various purposes by different agencies in the context of patients on ART. Therefore, each system has been used in various clinical trials and observational studies but there is currently no consensus on an internationally validated system. Because of this lack of standardization, comparisons between settings remain limited. This diversity highlights the need to harmonize practices related to ADR grading. It is also noteworthy that there was minimal feedback provided by the national PV centre thus highlighting the need to improve communication between this national authority and health care providers. In Côte d'Ivoire, the DPM is the only authority responsible for collecting adverse events and disseminating information to external partners, national health authorities and health professionals. The DPM is supported in its missions by the clinical pharmacology unit in charge of assessing the involvement of suspected drugs for any adverse event notification and located at the Faculty of Medicine. Infrastructure and human resources necessary for the development of PV do exist but are limited by a lack of a legal framework. Several actions have been taken to enhance PV activities such as the membership of Côte d'Ivoire to the WHO program for international drug monitoring as an associate members since 2007 [12]. By providing evidence of a lack of knowledge concerning PV, this study might help national authorities to highlight the importance of monitoring for safety, especially in the context of ART scale-up. Although being a worldwide problem, under-reporting of ADRs is of particular importance in resource-limited settings where other challenges such as the lack of diagnostic capacities already limit the implementation of a reliable ADRs surveillance system. This barrier to PV activities could be amenable to relatively cheap strategies such as training courses. Indeed, previous reports from Africa showed that interventions to sensitize medical doctors to ADR notification significantly improved reporting [13–15]. Thus, a dedicated training in PV is needed before advertising for ADR monitoring of HIV-infected patients. So far, PV in Africa has mainly been developed within malaria control programs [7, 8, 16, 17]. Collaboration between vertical programs providing medications on a large scale such as malaria, HIV/AIDS and to a lesser extent tuberculosis should be enforced as they share the same challenges in the surveillance of ADRs.

Adverse drug reaction monitoring

Our first finding related to passive ADR monitoring, was that there was some capacity of the selected participating HIV centers to use treatment modification/interruptions as a proxy for ADR monitoring. Indeed, the reason of treatment modification/interruptions was relatively well documented with less than 8% of missing values based on a retrospective medical chart review. The reporting of ADRs based on treatment modification/interruptions might not reflect the true occurrence of ART toxicity as some toxicity such as anemia or peripheral neuropathy are more often associated with treatment modifications than others such as gastrointestinal disorders [18]. This approach is also limited by its inability to detect low grade and unexpected ADRs. Nevertheless, it is probably the most feasible method to monitor ADRs in large observational HIV cohorts and it is also a key indicator for the maintenance of drug supplies in HIV programs [4, 19]. Despite being programmatic key indicators, there are currently no specific recommendations related to the monitoring of ADRs in national HIV guidelines of Côte d'Ivoire [20]. There are, thus, challenges in trying

to improve routine collection of ART toxicity by prescribers in medical charts and providing the necessary resources for data entry in HIV clinics.

The overall incidence estimates of ADRs were significantly lower than in a previous report from one of our participating HIV centers where Messou *et al* found an incidence of ADR-related treatment modification/interruptions of 12.4/100 PY during the first year after ART initiation [4]. Taking into account the time since ART initiation, we observed a quite similar incidence of ADRs in patients exposed to ART for <1 year (12.5/100 PY) and a four-fold decrease in the incidence of ADRs in patients exposed to ART for ≥1 year (2.9/100 PY) confirming that the major part of ADR-related treatment modification/interruptions occurs during the early period of ART treatment [5, 21]. A different ADR distribution was observed according to the duration of ART exposure. While cutaneous reactions and hematological disorders occurred frequently in patients exposed to ART for <1 year, lipoatrophy occurred exclusively in patients exposed to ART for ≥1 year as described elsewhere [22]. Stavudine, only available as a fixed-dose combination, was the most commonly identified drug associated with ADR-related treatment modification/interruptions, irrespectively of time since ART exposure. This finding is consistent with the predominant use of stavudine-containing first line ART regimens in most African settings compared to other resource-limited settings [23]. According to the 2010 update of the WHO guidelines, countries using stavudine in first-line regimens should now start phasing it out in favor of other nucleoside reverse transcriptase inhibitors such as zidovudine or tenofovir because of its toxicity [24]. Access to these alternate medications will thus need a particular effort of safety monitoring. Peripheral neuropathy was the most reported ADR, stavudine being the usual withdrawn drug in case of peripheral neuropathy. Surprisingly efavirenz, nevirapine and indinavir were also largely withdrawn in case of peripheral neuropathy. Although peripheral neuropathy has been already associated with non nucleoside inhibitors of the reverse transcriptase and protease inhibitors, this should remain relatively rare compared to its occurrence after exposure to nucleoside inhibitors of the reverse transcriptase [25]. These findings raise concerns about the causality assessment in clinical practice and reinforce the need to implement PV activities in HIV care programs. Specific features associated with the use of antiretroviral drugs (i.e. generally prescribed as fixed-dose combinations in order to simplify pills intake and improve adherence, must be given daily and for life) raises specific challenges for causality assessment and stresses the need for a careful training of pharmacologists. Recently WHO has promoted PV activities for ART, bringing together PV and HIV specialists to develop formal propositions to enhance ADR monitoring in HIV cohorts in resource-limited settings [26]. These guidelines for monitoring ART-related ADRs need now to be applied in the field.

Limitations

As the assessment of ART prescribers for PV activities was conducted on a convenience sample, results highlighted in this report might not represent the exact level of knowledge in ART-related PV in Abidjan as well as in the rest of the West African region. Nevertheless, as we involved a wide range of HIV clinics including the two largest ones in the urban area of Abidjan, we believe that this description has at worst over-estimated knowledge towards PV, thus enforcing the need for a wide and decentralized enhancement of PV activities in this part of the world.

Even if a good quality control system is implemented to avoid reporting biases, using ART treatment modification/interruptions to monitor toxicity in HIV-infected patients has several limitations. First of all, fatal ADRs and ADRs in patients who are lost to follow-up are likely to be missed in such a system, thereby under-estimating the rate of ADRs. Secondly, it does not take into account toxicity related to other therapeutics such as antibiotics or traditional medicines. Third, it does not take into account mild adverse reactions that could not induce

treatment modification/interruptions but could affect the adherence to ART. Thus, other methods to collect ADRs in patients on ART need to be implemented. A third approach was initially designed to monitor ADRs. Clinical monitors in charge of collecting ADRs were asked to prospectively and actively solicit ART prescribers to collect severe and unexpected ADRs by performing a weekly visit to HIV clinics. Facing their lack of availability and unwillingness to allocate more time to this specific task, this prescribers-based active surveillance of ADR could not be set-up, demonstrating the limitations faced in enhancing the capacity for monitoring unexpected ADRs.

Conclusions

This pilot study highlighted several barriers currently limiting PV activities in HIV clinics in Côte d'Ivoire. First, the lack of knowledge of ART prescribers concerning ADR staging and reporting prevents the implementation of spontaneous ADR notification, the cornerstone for monitoring unexpected or low grade adverse events. Secondly, the routine collection of ADR-related treatment modification/interruptions is feasible but improvements concerning how information on drug-related adverse events is collected are required to respond to some of the key research questions related to known and suspected drug toxicities in the context of ART scale-up in Africa. Resource allocation needs now to focus on these priorities.

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Appendix

The Adult Group of the International epidemiological Database to Evaluate AIDS (IeDEA) West Africa Collaboration was constituted as follows in 2008–2009:

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 - ANRS 1215 Cohort, Dakar, Senegal
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 - Fajara Cohort, Banjul, Gambia
 - Service de Médecine Interne, CNHU Hubert Maga, Cotonou, Benin
 - Service de Médecine Interne, CHU Yalgado, Ouagadougou, Burkina-Faso
- **Coordinating centers**

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Key points

- While antiretroviral treatment (ART)-related adverse drug reactions are documented in industrialized countries, there is no adverse drug reactions surveillance system dedicated to ART in most African countries
- In the present study, we assessed the capacity of a selected subset of HIV clinics in Abidjan, Côte d'Ivoire to conduct pharmacovigilance activities for ART
- The lack of knowledge of ART prescribers concerning adverse drug reactions staging and reporting prevents the implementation of spontaneous adverse drug reactions notification
- Using treatment modification/interruptions for adverse drug reactions monitoring appears feasible but improvements are needed to respond to key questions related to drug toxicities in the context of ART scale up in Africa

Table 1

Knowledge and practices of ART prescribers according to their workplace (referral hospital versus other HIV clinical centers). leDEA West Africa, Abidjan, Côte d'Ivoire, March 2009.

Duration of ART prescription in months (median, IQR)	ART prescribers from referral hospital wards (N=48)			ART prescribers from other wards (N=33)			P	Total (N=81)
	n	(%)		n	(%)			
Prescribers who declared grading ADRs	37	(77.1)		19	(57.6)		0.06	56 (69.1)
Type of grading system(s) usually applied* :								
WHO	17	(41.5)		6	(31.6)		0.46	23 (38.3)
ANRS	7	(17.1)		5	(26.2)		0.31	12 (20.0)
ACTG	11	(26.9)		1	(5.3)		0.05	12 (20.0)
DAIDS	3	(7.3)		1	(5.3)		0.62	4 (6.7)
IMPAACT	1	(2.4)		0	(0)		0.68	1 (1.7)
No precision	2	(4.8)		6	(31.6)		0.01	8 (13.3)
Prescribers who currently notify ADRs	7	(14.6)		5	(15.1)		0.41	12 (14.8)
Ever heard about PV	37	(77.1)		28	(84.8)		0.39	65 (80.2)
Knowledge of a national PV center	12	(25.0)		11	(33.3)		0.94	23 (29.4)
Ever filled-in a dedicated ADR notification form	3	(6.2)		6	(18.2)		0.01	9 (11.1)
Ever had a feed back information from the national PV center	0	(0.0)		3	(9.1)		0.06	3 (3.7)

* Question asked to the 56 prescribers currently grading ADRs, more than one grading system could be stated, eight of them did not answer. ART: antiretroviral therapy, ADR: adverse drug reactions, PV: pharmacovigilance, IQR: inter quartile range, WHO: World Health Organization, ANRS: <<Agence Nationale de Recherches Sur le SIDA et les hépatites virales >>, ACTG : AIDS Clinical Trial Group, DAIDS: Division of Acquired Immunodeficiency Syndrome, Impact: International Maternal Pediatric Adolescent AIDS Clinical Trial Group

Table 2

Distribution of retrospectively reported ADRs according to their suspected associated antiretroviral drugs in three HIV cohorts from the IeDEA West Africa collaboration, Abidjan, 2008.

	Antiretroviral drugs(s) withdrawn								Total [†]
	Stavudine	Nevirapine	Zidovudine	Efavirenz	Indinavir	Stavudine+Nevirapine	Zidovudine+Lamivudine	Other drugs [*]	
ADR retrospectively identified	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Peripheral neuropathy	57 (46.4)	19 (15.4)	8 (6.5)	10 (8.1)	5 (4.1)	8 (6.5)	3 (2.4)	13 (10.6)	123 (100)
Cutaneous reaction	19 (43.2)	2 (4.5)	4 (9.1)	4 (9.1)	11 (25.0)	3 (6.8)	0 (0.0)	1 (2.3)	44 (100)
Hematologic disorders	12 (60.0)	0 (0.0)	3 (15.0)	2 (10.0)	0 (0.0)	0 (0.0)	2 (10.0)	1 (5.0)	20 (100)
Lipodystrophy	7 (36.8)	2 (10.5)	3 (15.8)	3 (15.8)	0 (0.0)	0 (0.0)	3 (15.8)	1 (5.3)	19 (100)
Central nervous disorders	7 (38.9)	5 (27.8)	3 (16.7)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.0)	18 (100)
Gastrointestinal disorders	6 (33.2)	3 (16.7)	5 (27.8)	3 (16.7)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	18 (100)
Hepatic toxicity	5 (50.0)	1 (10.0)	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	10 (100)
Cardiac toxicity	5 (83.3)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (100)
Other ADRs [‡]	6 (60.0)	2 (20.0)	1 (10.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (100)
Total [§]	124/3323	34/2488	29/1831	25/2177	17/253	12/2374	8/1792	19 [*]	268/5252

ART: Antiretroviral treatment. ADR: Adverse Drug Reaction.

^{*} Other drug(s) withdrawn: 7/2374 stavudine+lamivudine+nevirapine, 5/775 stavudine+efavirenz, 3/18 abacavir+didanosine, 2/3268 stavudine+lamivudine, 2/88 abacavir.

[†] Total number of withdrawn drugs: 268 of the 273 ADR-related treatment modifications for which the antiretroviral drug(s) withdrawn were notified in the medical charts.

[‡] Other ADRs: lactic acidosis, nephrotic syndrome, chest tightness, ocular lesion, diffuse pain.

[§] total number of withdrawn drug(s)/total number of patient exposed to the antiretroviral drug(s) withdrawn, as multiple exposure to antiretroviral drugs is likely, the sum of these denominators is not equal to the total number of patients exposed.