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SHORT COMMUNICATION

Safety and Effectiveness of Highly Active Antiretroviral Therapy in Treatment-Naïve HIV Patients: Preliminary Findings of a Cohort Event Monitoring Study in Belarus

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Abstract

Background and Objective Antiretroviral drugs have well-documented evidence-based favorable benefit–risk ratios. Although various studies have investigated and characterized the safety profile of antiretroviral medicines, there are a limited number of studies evaluating the safety of first-line antiretroviral therapy (ART) in patients with a specific co-morbidity. A cohort event monitoring (CEM) study of the safety and effectiveness of antiretroviral medicines in a target population that has a significant level of co-morbidities (chronic infectious diseases, peripheral blood cytopenias) was implemented. The aim was to evaluate the safety profile of the highly active ART (HAART) in the target population and subpopulations with risk factors, to optimize the monitoring and decision-making procedure for subgroups of patients with specific types of co-morbidity, and to implement a more vigilant approach to therapy management in risk groups of patients.

Methods Prospective observational CEM was implemented among HAART-naïve HIV-positive patients at four clinical sites from December 2012. Eligible patients were those starting first-line HAART. Close medical supervision of all enrolled patients, with regular clinical and laboratory monitoring, was provided by healthcare professionals within 1 year after commencement of therapy. Standardized forms were used for data collection on initial and subsequent visits. All objective or subjective deviations in

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Key Points

Patients with HIV infection could have country-specific population characteristics, which could modify antiretroviral therapy safety, effectiveness, patients' compliance, and compromise the medical program.

Implementation of cohort event monitoring (CEM) in public health programs is especially valuable.

CEM is an effective tool for safety and effectiveness monitoring.

CEM allows the gathering of important safety data in country-specific settings and encourages health professionals to report adverse reactions, contributing significantly to establishing pharmacovigilance in critical healthcare spheres.

condition (events) were assessed for a causal relationship with ART, and for severity, seriousness, reversibility, preventability, and pre-existing risk factors in the case of adverse drug reactions (ADRs).

Results A total of 518 HAART-naïve HIV-positive patients were enrolled in the CEM study. Of these patients, 65 % (337) experienced one or several ADRs related to one or more components of HAART. Most of the ADRs reported were non-serious, expected, common (very common), transient (correctable), or reversible. The most common were hematotoxic, hepatotoxic, and neurotoxic adverse reactions. In several cases, some types of toxicities, associated with zidovudine, efavirenz, and nevirapine, had a high level of severity, necessitating hospitalization and drug regimen or single-agent substitution. Severe cases of hematological, hepatobiliary, and psychiatric toxicities were associated with pre-existing risk factors.

Conclusion CEM is an effective tool for safety and effectiveness monitoring and could be successfully implemented for intensive study of important safety issues and for overcoming knowledge gaps regarding safety. In order to achieve a favorable benefit–risk ratio for HAART in the specific sections of the population with pre-existing risk factors for development of ART toxicities, more vigilant consideration and careful assessment before therapy is commenced and further regular monitoring of key laboratory parameters is required.

1 Introduction

Highly active antiretroviral therapy (HAART) is effective in decreasing the plasma HIV viral load. The introduction of HAART has led to a significant decline in morbidity and mortality among HIV-infected patients [1, 2]. Antiretroviral drugs have well-documented evidence-based favorable benefit–risk ratios. However, the toxicity associated with many antiretroviral drugs often leads to discontinuation or changes in treatment, which could limit a patient's adherence and, therefore, virological effectiveness [3, 4]. The toxicity profile of antiretroviral drugs could be significantly modified by individual factors, such as concomitant pathology and related concomitant medication. HAART adherence could be affected by associated adverse reactions [4], as well as by sociodemographic and psychosocial patient factors [5]. These factors predispose to significant variability of the safety and effectiveness of HAART among different patient populations and, thus, require further optimization of the therapeutic strategy and safety monitoring approach. Although various studies have investigated and characterized the safety profile of antiretroviral medicines, there are a limited number of studies evaluating the safety profile of first-line HAART in patients with specific profile-modifying concomitant pathology. In addition, the majority of known data on adverse drug reactions (ADRs) are derived from cohort studies or clinical trials conducted in North America, Europe, and Australia, and are based on innovator drug products. It is vital to gather data on ADRs in resource-limited settings, since different populations with different co-morbidities are being treated than in resource-rich countries [6]. In the Republic of Belarus, the population of patients living with HIV is characterized by a high level of several specific co-morbid conditions, such as hepatitis C and B virus and tuberculosis (TB) infection (including multidrug-resistant TB). With support from the Monitoring Medicines Programme funded by the Seventh Framework Programme (FP-7) of the Research Directorate of the European Commission [7], World Health Organization (WHO), and the Uppsala Monitoring Centre, Sweden (UMC), we have initiated a cohort event monitoring (CEM) study of HIV-positive individuals, naïve from antiretrovirals at enrolment, to evaluate the safety profile of HAART in a target population and subpopulations with risk factors, optimize the monitoring and decision-making process for subgroups of patients with a specific co-morbidity, and evaluate the factors influencing the compliance and effectiveness of HAART in the target population. 'Active' pharmacovigilance surveillance methods, including CEM, have several advantages that help to overcome many deficiencies of spontaneous reporting, on which the majority of pharmacovigilance activity depends [9]. An important objective of this CEM study was to implement an effective system of continuous safety/effectiveness monitoring and ADR reporting among healthcare providers (HCPs) in public health programs.

2 Methods

A CEM (observational, prospective epidemiological) study was initiated among HAART-naïve HIV-positive patients at four clinical sites (Minsk Infectious Hospital, Gomel Regional Infectious Hospital, Soligorsk Central Regional Hospital, Zhlobin Central Regional Hospital) in the Republic of Belarus from December 2012. CEM methodology, data collection tools, data processing, and data analysis were based on WHO recommendations [9, 10]. Treatment-naive patients with a CD4 count $\leq$350 cells/mm^3, HIV clinical stage 3 or 4, or concomitant TB infection irrespective of CD4 count who were a minimum age of 18 years and had started HAART were enrolled in the cohort.

Antiretroviral therapy (ART) admission and monitoring was performed according to the national guideline for the start of HAART in HIV-infected patients, which is based on WHO recommendations [11]. The antiretroviral medicines being monitored included two first-line ART

regimens based on two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-NRTI: zidovudine + lamivudine + efavirenz (nevirapine) [AZT + 3TC + EFV (NVP)] or tenofovir + lamivudine + efavirenz (nevirapine) [TDF + 3TC + EFV (NVP)]. Special CEM data collection forms were used for clinical and laboratory data capture before starting HAART and within the subsequent 1-year monitoring period (see Electronic Supplementary Material 1 and 2). Evaluation of the safety and effectiveness of ART via collection of clinical and laboratory data was performed on monitoring visits at 4 weeks, 8 weeks, and every subsequent 12 weeks after starting therapy. The initial assessment before starting ART (point 0) included evaluation of the current clinical status of the patient, collection of a medical history (all co-morbid conditions), laboratory testing for virological markers [HIV (hepatitis B surface antigen) serology, HIV viral load], immunological markers (CD4 lymphocyte count), and basic hematological, hepatological, renal, pancreatic, and metabolic functional parameters (hemoglobin, white blood cell count, platelet count, ALT, AST, serum creatinine, serum amylase, bilirubin, fasting serum cholesterol). The treatment initiation form included information about concomitant medicines (including herbal medicines and dietary supplements) taken at any time during the 30 days before initiation of ART. The treatment review form included a description of any signs or symptoms (clinical events) experienced by the patients after commencement of ART as a subjective and objective deviation from the previous state, including laboratory testing of basic functional laboratory parameters. HAART effectiveness monitoring was performed by regular testing of virological markers (viral load) and immunological markers (CD4 lymphocyte count). Any untoward, unfavorable, and unintended medical occurrence (sign, symptom, disease) in patients enrolled in the monitored cohort, temporally associated with the administration of ART, was evaluated as an adverse event to antiretroviral medicines and underwent further evaluation for severity, seriousness, or causal relationship with components of ART. Severity assessment was performed using Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [12]. Standardized case causality relationship assessment was performed according to WHO–UMC causality categories [8] and the Naranjo Adverse Drug Reaction Probability Scale [9, 13]. Seriousness was assessed according to internationally used terminology for serious adverse reactions [14]. Categorization of the detected ADR according to its frequency was performed according to the Council for International Organizations of Medical Sciences (CIOMS) III Working Group recommendations [15]. The CemFlow web-based data management tool, provided by the UMC, was used for data management and analysis. ADR reporting activity of HCPs was evaluated according to the number and quality of ADR reports submitted from the clinical sites.

3 Results

3.1 Characteristics of the Study Population

A total of 518 HAART-naïve HIV-positive patients were enrolled in the CEM, of whom 303 (58.5 %) were males and 215 (41.5 %) were females. The age of participants ranged from 20 to 65 years (Table 1). The majority of study participants were urban residents.

A significant proportion of patients had co-infections, co-morbidities, and changes in hematological or functional parameters before starting ART monitoring (Table 2).

Administration of first-line ART regimens was based on a physician's judgment and followed the national guideline for initiation of highly active antiretroviral treatment (HAART)

Table 1 Socio-demographic and clinical characteristics of highly active antiretroviral therapy-naïve HIV-positive patients participating in cohort event monitoring of antiretroviral therapy

Variables	Frequency	%
Sex		
Male	303	58.5
Female	215	41.5
Age (years)		
20–29	108	20.8
30–39	262	50.5
40–49	107	20.6
50–59	34	6.6
60 and above	7	1.5
HIV clinical stage		
1	168	32.5
2	123	23.5
3	83	15.9
4	144	27.8
CD4 count (cells/mm^3)		
≤200	289	55.7
≥200	229	44.3

Table 2 Prevalence of hepatitis C, tuberculosis, anemia, thrombocytopenia, and leukopenia among highly active antiretroviral therapy-naïve HIV-positive patients participating in cohort event monitoring of antiretroviral therapy

Co-morbidity	Frequency	%
Hepatitis C	220	42.5
Tuberculosis	65	12.5
Anemia	69	13.3
Thrombocytopenia	122	23.6
Leukopenia	80	15.4

Table 3 Antiretroviral drug regimens at enrollment

ART regimens	Frequency	%
AZT + 3TC + EFV	371	71.6
TDF + 3TC + EFV	71	13.7
AZT + 3TC + NVP	69	13.3
TDF + 3TC + NVP	7	1.3

3TC lamivudine, *ART* antiretroviral therapy, *AZT* zidovudine, *EFV* efavirenz, *NVP* nevirapine, *TDF* tenofovir

Table 4 List of the most common concomitant medications

ATC pharmacological/therapeutic subgroups	International Nonproprietary Names
Drugs for treatment of tuberculosis	Amikacinum, amoxicillin clavulanic acid[a], capreomycin, cycloserine, ethambutol, izoniazid, levofloxacine, ofloxacine, para aminosalicylic acid, protionamide, pyrazinamide, rifampicin
Antimycotics for systemic use	Fluconazole[b]
Antibacterials for systemic use	
Macrolides, lincosamides, and streptogramines	Azithromycin[b]
Sulfonamide and trimethoprim	Sulfamethoxazole and trimethoprim[c]
Antianemic preparations	Ferric oxide polymaltose complexes
Antiepileptics	Carbamazepine
Bile and liver therapy	Ursodeoxycholic acid, silymarin

ATC Anatomical Therapeutic Chemical classification

[a] Repurposed drug for therapy of multidrug-resistant forms of tuberculosis

[b] Prophylaxis of opportunistic infections

[c] Co-trimoxazole preventive therapy

in HIV-infected patients. Distribution of patients between the ART regimens at enrollment is shown in Table 3.

The majority of the enrolled patients received different concomitant medications, which varied significantly depending on indications. The most common concomitant medications included therapy for prophylaxis of opportunistic infections, anti-TB therapy, supporting therapy (ADR symptomatic treatment and management), and opioid substitution therapy (Table 4).

3.2 Patient Follow-Up and Survival

According to the intermediate data of the 518 patients enrolled in the study, 363 (70.1 %) completed the planned 48 weeks of follow-up; 99 (19.1 %) patients were lost to follow-up. The reasons for dropout were non-compliance (39; 7.5 %), patient decision (31; 6 %), non-response to several invitations (15; 2.9 %), and moving away (14; 2.7 %). During the follow-up period 32 (6.2 %) of the enrolled patients discontinued or changed prescribed treatment because of ADRs, three (0.6 %) were withdrawn from monitored therapy due to ineffectiveness of the antiretroviral regimen, and 21 (4 %) of the 518 patients died.

3.3 Preliminary Antiretroviral Therapy Safety Monitoring Data

According to the intermediate results of ART safety monitoring, about 65 % (337) of patients experienced one or several ADRs related to one or more components of HAART. Most of the detected ADRs were non-serious, expected, common (>1/100 and <1/10) or very common (>1/10), transient (correctable), or reversible (Table 5).

Some of the ART-associated detected adverse reactions were evaluated as uncommon (>1/1,000 and <1/100) according to the current Summary of Product Characteristics (SPC) information (Table 6).

Serious adverse reactions experienced by the patients were evaluated as related to the three components of ART: zidovudine, nevirapine, and efavirenz (Table 7).

According to the intermediate results of ART toxicity monitoring, the following ADRs were experienced with a higher than expected rate: thrombocytopenia related to zidovudine (62 cases; 11.9 %), hallucinations related to efavirenz (seven cases; 1.3 %), and thrombocytopenia related to lamivudine (nine cases: 1.7 %). Several suspected adverse reactions, classified as unexpected, developed in close temporal relationship with the intake of a suspected component of ART (efavirenz): one patient experienced tongue numbness and one patient the loss of consciousness. In both cases, positive results of dechallenge and rechallenge were reported by the HCPs.

Additional safety findings related to the ART regimens could be of interest due to the shorter than expected reported time to onset. Two cases of fat maldistribution (lipoatrophy and lipodystrophy) were revealed after 8 and 2 months, respectively, following commencement of ART (AZT + 3TC + EFV). The case of lipoatrophy was associated with one of the known risk factors (CD4 count 185 cells/mm^3).

One case of cytomegalovirus retinitis, as a manifestation of immune reactivation syndrome, was detected in a causal relationship with the commencement of AZT + 3TC + EFV regimen.

3.4 Pharmacovigilance Activity

Implementation of CEM included intensive training of medical staff in detecting, evaluating, managing, and reporting ADRs. The monitoring team was involved in

Table 5 Non-serious expected common (very common) adverse reactions associated with the monitored first-line antiretroviral drugs

ARV drug	Abbreviation	Dosage	SOC	ADRs
Nucleoside reverse transcriptase inhibitors (NRTIs)				
Zidovudine	AZT	300 mg bid	Blood and lymphatic system disorders	Anemia, leukopenia
Lamivudine	3TC	150 mg bid	CNS and psychiatric disorders	Insomnia
			Gastrointestinal system disorders	Diarrhea
Tenofovir	TDF	300 mg od	Gastrointestinal system disorders	Vomiting, nausea
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Nevirapine	NVP	200 mg od for 2 weeks, then increased to 200 mg bid	Skin and subcutaneous system disorders	Rash, including severe forms (generalized form, maculopapular form, confluent rash)
			Immune system disorders	Angioedema
			Hepatobiliary disorders	ALT, AST increased, hepatitis
			Gastrointestinal system disorders	Vomiting
			CNS and psychiatric disorders	Headache
Efavirenz	EFV	600 mg od or 300 mg bid	CNS and psychiatric disorders	Dizziness, headache, somnolence, abnormal dreams
			Gastrointestinal system disorders	Vomiting, nausea, abdominal pain, serum alpha-amylase increased
			Skin and subcutaneous system disorders	Rash (including maculopapular skin eruptions) from mild to severe forms, pruritus
			Hepatobiliary disorders	ALT, AST increased
			General disorders	Fatigue

ADR adverse drug reaction, *ARV* antiretroviral, *bid* twice daily, *od* once daily, *SOC* System Organ Class

Table 6 Non-serious expected uncommon adverse reactions associated with the monitored first-line antiretroviral drugs

ARV drug	Abbreviation	Dosage	SOC	ADRs
Nucleoside reverse transcriptase inhibitors (NRTIs)				
Zidovudine	AZT	300 mg bid	Blood and lymphatic system disorders	Thrombocytopenia
			General disorders	Lipoatrophy, lipodystrophy
Lamivudine	3TC	150 mg bid	Blood and lymphatic system disorders	Thrombocytopenia, anemia, leukopenia
Tenofovir	TDF	300 mg od	Renal and urinary disorders	Creatinine increased
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Efavirenz	EFV	600 mg od or 300 mg bid	CNS and psychiatric disorders	Hallucinations, confusional state, balance abnormal, ataxia
			Vascular disorders	Flushing
			Eye disorders	Vision blurred
			Metabolism and nutrition disorders	Hypercholesterolemia

ADR adverse drug reaction, *ARV* antiretroviral, *bid* twice daily, *od* once daily, *SOC* System Organ Class

further investigations and following up adverse reactions reported from the health facilities. The pharmacovigilance center, coordinator, and review panel periodically evaluated the monitoring system with assessment of the reporting activity (for completeness, timeliness, accuracy), case management, and follow-up. A significant increase in the absolute number of ADR reports, as one of the indicators of pharmacovigilance activity, was associated with active surveillance implementation (Table 8). HCPs demonstrated a more vigilant approach to detection of

Table 7 Serious expected adverse reactions associated with the monitored first-line antiretroviral drugs

ARV drug	Abbreviation	Dosage	SOC	ADRs
Nucleoside reverse transcriptase inhibitors (NRTIs)				
Zidovudine	AZT	300 mg bid	Blood and lymphatic system disorders	Severe anemia, thrombocytopenia, thrombocytopenia with hemorrhagic syndrome
			Skin and subcutaneous system disorders	Severe atopic dermatitis, complicated with microbial eczema
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Nevirapine	NVP	200 mg od for 2 weeks, then increased to 200 mg bid	Immune system disorders	Severe generalized form of rash with concomitant severe hepatitis, generalized skin reaction with hyperthermia, angioedema, generalized skin reaction
			Hepatobiliary disorders	Severe hepatotoxic reaction, jaundice, severe hepatitis
Efavirenz	EFV	600 mg od or 300 mg bid	Hepatobiliary disorders	Severe hepatitis (resulting in hospital admission)
			Skin and subcutaneous system disorders	Rash generalized (resulting in hospital admission)
			CNS and psychiatric disorders	Severe headache (resulting in hospital admission), convulsions
			Eye disorders	Blurred vision (resulting in hospital admission)

ADR adverse drug reaction, *ARV* antiretroviral, *bid* twice daily, *od* once daily, *SOC* System Organ Class

Table 8 Adverse drug reaction reports submitted from the clinical sites

Clinical site	2012	2013	2014
Minsk Infectious Hospital	7	16	34
Soligorsk Central Regional Hospital	1	52	65
Gomel Regional Infectious Hospital	0	75	59
Zhlobin Central Regional Hospital	0	30	46
Total	8	173	204

ADRs, actions taken, and implementation of risk-minimization activity. Sustainability of the impact of CEM on reporting activity will be evaluated regularly over the next 3 years.

4 Discussion

The final assessment of the safety, effectiveness, and therapy compliance data for the monitored medicines will be performed after completing the follow-up period in 2015. According to the intermediate data of ART safety monitoring within the present cohort study, the safety profiles of the ART components were consistent with the expected results for the general population of HIV-infected patients. However, some types of toxicities associated with zidovudine, efavirenz, and nevirapine had, in several cases, a high level of severity, required hospitalization, and drug regimen or single-agent substitution. Severe cases of hematological, hepatobiliary, and psychiatric toxicities were associated with pre-existing risk factors: baseline anemia or thrombocytopenia, CD4 count $\leq$200 cells/mm^3, underlying hepatic disease, chronic co-infections, concomitant use of hepatotoxic or neurotoxic drugs, opiate or alcohol abuse, underlying mental disorders, or traumatic brain injury. A favorable individual ART benefit–risk ratio for every patient is of paramount importance. Therefore, for each sub-population of patients with pre-existing risk factors for potentially serious but manageable types of toxicities, initial assessment via administration of the regimen with the lowest risk of the relevant adverse reactions, and further close monitoring of key laboratory parameters, could be considered as an essential component of the care of patients with a high risk of adverse reactions and should be a routine element of risk-minimization measures.

Poor adherence to long-term therapy severely compromises the effectiveness of treatment, making this a critical issue in population health. Preliminary data from this study showed that the most common factors affecting compliance with ART included ADRs, alcohol/narcotic abuse, fear of ADRs, low social status (influence of social environment), having too many medicines to take, difficulties associated with daily life, and the patient's personal characteristics (forgetfulness). Final analysis of the study results is planned to include detailed evaluation of the factors contributing to non-compliance, categorization, and identification of possible actions for improving patient adherence to ART.

Challenges in implementation of CEM in Belarus include the significant routine workload of HCPs and pharmacovigilance staff, difficulties with follow-up of some of the cohort (drug abusers, alcohol abusers, patients with low social status), and unpredictable staff changes. CEM is a significantly more resource-consuming method than spontaneous reporting. However, all potential possibilities and the quality of the data that could be obtained make this tool, in the case of a properly established cohort, comparable to clinical trials. Maximum benefit of this tool may be achieved when used in specific subpopulations or within a specific medical intervention characterized by definite limitations of safety/effectiveness evidence data and requiring more intensive safety and effectiveness monitoring. The benefit is significantly increased when this tool is used in settings with low levels of routine pharmacovigilance activity, as it can help to implement an ADR reporting culture and appropriate safety management into routine clinical practice.

The present study has several limitations relating to sample size, representativeness of the study population (selection bias), and the dropout rate. The relatively small sample size (518 patients) for the subgroup analysis may not allow precise estimates. Selection bias may occur due to the dropout minimization approach and non-inclusion in the cohort of some patients with a very high risk of loss to follow-up (e.g., socially disadvantaged patients, patients with severe drug and/or alcohol dependencies). This could result in a difference in the incidence of the outcomes of interest between those who participated in the CEM and those who did not. By examining the characteristics of dropouts, the reasons for loss of subjects will be identified, including those factors that are related to the outcomes of interest, and the level of bias related to this limitation will also be evaluated.

5 Conclusion

CEM is an effective tool for safety and effectiveness monitoring and could be successfully implemented for intensive study of important safety issues and filling safety knowledge gaps. For the specific part of the population with pre-existing risk factors for development of ART toxicities, achievement of a favorable benefit–risk ratio for HAART could require more vigilant consideration and careful assessment before therapy commencement and further regular monitoring of key laboratory parameters. Active safety monitoring methods contribute to the improvement of patient care and optimization of pharmacotherapy and help to implement pharmacovigilance into routine medical practice.

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