CEM in Belarus. **Project history**

**Monitoring Medicines Programme 7 (Seventh Framework Programme)**

*The general aim:* to reduce patient deaths and negative health impacts arising from undetected medicines safety problems globally

1 *from 4 objectives:* develop additional methods to complement data from spontaneous reporting system.

Plan has been conceived and written by **Dr. Shanthi Pal, WHO**, submitted and approved by EC, grant agreement applicable from 1 September 2009. Coordination functions – **UMC (Dr. Sten Olsson)**.
CEM in Belarus. **General goals**

- Improving of patients care and ART safety/efficacy taking into account comorbidity and social specificity of every patient.
- Increasing of reporting activity among ART HCP, implementation of ART reporting system that receives information that can be used to improve patient safety.
- Implementation of the effective system of continuous safety/efficacy ART monitoring and assurance of safety of HIV-infected patients.
- Implementation of the effective system of early warning of problems related to the use of medicines.
- Encouraging the safe, rational and more effective use of ARV drugs.
- Contributing to the assessment of benefit, harm, effectiveness and risk of medicines used in HIV-infected patients, leading to the prevention of harm and maximization of benefit.
- Promote understanding, education and training and pharmacovigilance and its effective communication to the public.
CEM in Belarus. **Objectives of the project**

- Evaluation of the incidence rates for adverse events in patients admitted to ARV therapy.
- Characterization of known adverse reactions experienced by the patients on ARV therapy.
- Signal detecting of previously unrecognized adverse reactions.
- Interactions with other medicines, food additives and food components.
- Identifying of ADR risk factors in patients admitted to ART, development of risk minimization measures.
- Data obtaining for ARV drugs safety and efficacy profile of antiretroviral therapy in patients with specific for our region comorbidities (TB, especially MDR forms of TB; HCV); development of optimal individual combination pharmacotherapy and safety/efficacy monitoring approach for this population.
CEM in Belarus. **Objectives of the project (2)**

- Development of optimal monitoring and pharmacotherapy decision-making procedure for specific groups of patients with concomitant pathology.
- Data obtaining for ARV drugs safety profile characterization in specific population subgroups (pregnancy and lactation).
- Data obtaining for development of optimal pharmacotherapy approach for patients with rare locally specific comorbidity combinations.
- Evaluating of risk attributed to various ART regimen, providing a measure of comparative risk.
- Detecting of ART inefficacy, revealing of inefficacy reasons (faulty administration, substandard/counterfeit formulations, interactions, distribution/storage deviations), development and implementation of corrective and preventive measures.
- Evaluating of the factors influencing the compliance of ARV therapy.
- Providing international societies and pharmacovigilance system with information related to the ART safety and efficacy specific issuers, which could be important for other regions with similar comorbidity and social peculiarities.
CEM in Belarus: **Specificity of HIV-infected population**

- High level of concomitant HCV infection: about 55-60% of HIV-infected patients have HCV co-infection
- High level of tuberculosis infection in HIV-infected persons
- High level of MDR tuberculosis among HIV-infected patients: level of multidrug-resistant form of tuberculosis among newly diagnosed up to 33%, among people living with HIV and TB, 75% have MDR TB form
- According to cumulative data 47.5% of all HIV cases is intravenous drug users
CEM in Belarus. Project initiation and dynamics

Chronology of the HIV CEM Programme initiation

- **January of 2012** – development of the Programme and submission for WHO expert approval
- **April of 2012** – WHO and UMC - decision to reward project of CEM implementation in the Republic of Belarus
- **September of 2012** – starting of the preparatory phase
- **December of 2012** – final training of monitoring and phv team; starting of the pilot phase
- **January of 2013** – implementation of CEM in all sentinel sites
CEM in Belarus: CEM cohort

- **Monitored patients:**
  - HIV-infected, treatment-naive patients with CD4 count $\leq 350$ cells/mm$^3$ or with HIV clinical stage 3 or 4 irrespective of their CD4 count. Patients with HIV and TB irrespective of CD4 cell count.
  - Age from 18 years.
  - Clinically substantiated and followed national HIV therapy standards administration of one from the following ARVT first-line regimes:
    - **AZT+3TC+EFV(NVP) or TDF+3TC+EFV(NVP)**
  - Patient adequacy, supposed compliance, follow to recommendation, visits execution

- **Monitored medicines:**
  - **AZT+3TC+EFV(NVP) or TDF+3TC+EFV(NVP)**
CEM in Belarus. CEM design

CEM - observational (non-interventional), prospective, longitudinal, inceptional, dynamic, descriptive epidemiologic study – active safety monitoring tool

HIV infected patient → Inclusion-exclusion criteria evaluation → Yes → Patient enrollment, ID number, ID card, information → ARVT administration Initiation Form → Further visits (4w, 8w, every further 12 w) Safety/Efficacy ARVT evaluation Clinical events detecting/recording Review Forms on every visit

National PhV Center
All clinical events, including adverse events (expected, unexpected), abnormal changes in laboratory tests, lack of effectiveness, deterioration of concomitant pathology (onset, worsening, improvement), positive changes in pre-existing condition.
CEM in Belarus. **CEM Preparatory phase**

- Preliminary sentinel sites visits.
- Meetings in the MoH. MoH official approval – order of the MoH
- CEM printing materials (development, pretesting, printing)
- Trainings, workshops
- Initiating visits in pilot sentinel sites
- Launching of the CEM project
- *CemFlow* access and adaptation
- Starting of the pilot phase on two sentinel sites
CEM in Belarus. **Preparatory phase:**

**Preliminary sentinel site visits**

- Discussion of CEM project with sentinel site HCPs and top hospital management
- Evaluation: willingness, feasibility (professional, clinical/laboratory /diagnostic/technical facilities), eligibility (possibility to enroll required amount of the patients), understanding of the safety monitoring importance (safety motivation)
- Result: - 5 sentinel sites (*Minsk, Gomel, Zhlobin, Soligorsk, Svetlogorsk*) were identified as interested in CEM performing and has required resources and facilities
CEM in Belarus: Sentinel sites, HCP’s monitoring team

Minsk
Soligorsk
Zhlobin
Svetlogorsk
Gomel
CEM in Belarus. Preparatory phase. MoH: meetings, official approval
Confidentiality of data: DCFs include only ID number of the patients, no personal identification data are included.
CEM in Belarus. Other printing materials

- Patient ID card
- Guidelines for completion of TIF and TRF
- Code panel
- CEM performing guideline
- CEM poster
CEM in Belarus. **Preparatory phase:**

**Trainings, workshops**

**Training for Sentinel Sites HCPs:**


*Training for data entry personnel:*

use of *CemFlow* for data entry from DCFs; CEM conducting
CEM in Belarus. Preparatory phase results

- Five preliminary selected sentinel sites (Minsk infectious hospital, Gomel regional infectious hospital, Zhlobin central regional hospital, Svetlogorsk central regional hospital) were evaluated as an appropriate for participating in ART CEM project since meet requirements in respect to the human and material resources. All designated centers have been evaluated as feasible and eligible for CEM program implementation and performing.

- MoH official approval of the project implementation in the designated sentinel HIV monitoring clinical sites has been received, an appropriate order of the Ministry of Health has been signed by the Minister.

- All required printing materials (CEM DCFs, patient ID cards, CEM posters) and guidelines for CEM performing have been prepared and printed in appropriate amount.

- Necessary trainings and educational workshops for all CEM performing aspects for involved in CEM personnel were performed. HIV HCPs and data entry personnel are trained on CEM performing and ready to start project implementation.

- Two sentinel sites (Minsk infectious hospital and Zhlobin regional infectious hospital) are prepared for start the pilot phase of the project.

- Start of the project launched at 20th of December.

- CemFlow are installed and adapted for data input.

- Preparatory phase is closed, pilot phase is initiated.
CEM in Belarus. Pilot phase

- CEM project has started in two sentinel sites (Minsk infectious hospital and Zhlobin central regional hospital)

**Pilot phase results:**
- CEM project has been implemented in two clinical sites and there are any obstacles for further implementation in the other clinical sites;
- Two monitoring visits in the pilot centers have been performed;
- DCFs – are convenient and eligible data collection tool;
- Safety and efficacy monitoring adequately performed, events recorded;
- Changes in monitored medicines: ABC has been replaced with TDF due to the changes has been made in national HIV therapy standard (following changes in European recommendations) and changes in ARVT procurement situation;
- 16 patients have been enrolled in CEM during the pilot phase.

- Two initiation visits (Gomel – 29.01.2013, Soligorsk – 04.02.2013) have been performed. Sentinel sites were provided with required printing materials; additional training/consultation on working place have been performed and final evaluation made – sentinel sites are prepared for CEM program implementation.

* CemFlow has been tested with data entry of first DCFs, additional adaptation has been made.
CEM in Belarus. **Planning and monitoring (supervising)**

- **Patients enrollment:** about 60-70 patients per month to be enrolled

**Monitoring (supervising):**
- monitoring visits in 1 month after CEM starting in all sentinel sites (*end of February*) — *Interim report*
- monitoring visits 3rd month after starting (*end of April*) — *Interim report (May)*
- monitoring visits every next 3rd months on all sentinel sites and when necessary (*July-August, October-November, January*) — *Interim reports (September, December, February)*

- **Control parameters:**
  - number of patients enrolled
  - DCFs completion and sending to PhV Center
  - protocol fulfillment
  - adequate patient assessment
  - events recording
  - *CemFlow* data entry
  - data processing
  - procurement of material, technical and human resources.
CEM in Belarus. Planning and monitoring (2)

- **Closing of the patients enrollments:** 1 year after starting of the enrollment of HIV-infected patients (initiating and changing ART) in CEM study.

- **Final enrollment stage:**
  - Interim data analysis
  - Interim data interpretation
  - Interim CEM results

- **1-year follow-up (until February 2013):** 1-year follow up with every 3-months assessment. Data processing, entry in CemFlow, analyzing. **Control point:** half year after enrollment closing.

- **Closing of follow-up stage/CEM closing:**
  - Final data analysis
  - Data interpretation
  - CEM results
  - CEM results communication
CEM in Belarus. **Process of data analysis**

**NPvC**
Primary analysis of any clinical events in compare to previous state.
Double control (CEM coordinator and within data input) of any changes.
Basic analysis (seriousness, causality assessment,

**NPvC**
Regular meetings (1 time per 1,5-2 weeks) for data analysis with Clinical Supervisor; causality assessment, suspected ARVT component identifying, seriousness, expectedness, frequency, pharmacological assessment, risk factor, preventability
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CEM in Belarus. Intermediate data

- **Patient’s enrollment**: 453 (October of 2013)
- Share of the patients, withdrawn from the CEM – about 12%
  due to the following reasons:
  - *lack of compliance, lost of follow-up* – about 6%
  - *suspected ADR to one from monitored ARV drug and impossibility to administer the alternative CEM monitored ARV* – about 4%
  - *patient’s decision* – about 1%
  - *death of patients* – about 1%
- Change of ARVT due to ADR – about 4% from the total amount
CEM in Belarus: intermediate safety data

- The share of the patients, experienced ART related ADRs – about **36%**
- Most part of the revealed ADRs – non-serious and expected, common (very common), transient (correctable) or reversible

**AZT**
*Blood and lymphatic system disorders*: anemia, leucopenia

**EFV**
*CNS and psychiatric disorders*: dizziness, headache, somnolence, balance abnormal
*Gastrointestinal system disorders*: vomiting
*Skin and subcutaneous tissue disorders*: rash (mild-to-moderate maculopapular skin eruptions)
*Hepatobiliary disorders*: ALT, AST increased
*Laboratory tests abnormalities*: serum amylase increased

**NVP**
*Skin and subcutaneous tissue disorders*: rash
*Hepatobiliary disorders*: ALT, AST increased, hepatitis
*Gastrointestinal system disorders*: vomiting
*CNS and psychiatric disorders*: headache

**TDF**
*Gastrointestinal system disorders*: vomiting

**3TC**
*Nervous system disorders*: insomnia
CEM in Belarus: intermediate safety data

- **Not serious, expected, but uncommon ADRs:**
  - **AZT** - *Blood and lymphatic system disorders*: thrombocytopenia
  - **EFV** - *Psychiatric disorders*: hallucinations, confusional state
  - *Vascular disorders*: flushing
  - *Metabolism and nutrition disorders*: hypercholesterolemia
  - **TDF** - *Renal and urinary disorders*: creatinine increased
  - **3TC** - *Blood and lymphatic systems disorders*: thrombocytopenia

- **Serious expected** – 8 cases (4.9% from the total amount of ADR)
  - **AZT** - *Blood and lymphatic system disorders*: anemia (2); *Immune system disorder*: IRIS (?): Progressive multifocal leukoencephalopathy
  - **NVP** – *Immune system disorders*: severe forms of rash with concomitant hepatitis (1), generalized skin reaction with hyperthermia (1), angioedema (1), generalized skin reaction (2)
    - *Hepatobiliary disorders*: severe hepatotoxic reaction, jaundice, severe hepatitis (2)

- New safety information – suspected unexpected ADR (verification and expert evaluation) and suspected higher than expected ADR rate (verification and expert evaluation)

- ARVT effectiveness evaluation, virologic and immunologic response
  - Effectiveness/ineffectiveness of corrective measures
- Safety/effectiveness of ARVT in patients with numerous concomitant therapy
- Safety/effectiveness of ARVT in patients with concomitant pathology (tuberculosis, HCV etc.), dependencies (i/v drugs, alcohol)
- Adherence evaluation, reasons of incompliance
CEM in Belarus. **Challenges**

- Significant routine workload of the HCPs.
- Difficulties with follow-up for some share of the cohort (especially drug-abusers, alcohol-abusers), spending significant time and efforts for follow-up fulfillment.
- Unpredictable HCPs stuff changes.
CEM in Belarus. Lessons learned

- Integrating of stakeholders and partners efforts is extremely important. Support of the WHO (international and country level), MOH are essential especially in implementation stage.
- Monitored medicines – first-line with procurement guarantee.
- Involved HCPs – who in the routine practice follow safety monitoring recommendations, have patient-oriented approach.
- Workload optimizing: according to our experience an optimal amount of the monitored patients for one HCP – 100 patients, maximal – 150-170.
- In big sentinel sites it’s desirable to train and involve + one “reserve” HCP for case of stuff changes.
- Close feedback with HCPs (data clarification, clinical events discussion, organizational problems settling etc.)
- Priority to the basically compliant patients?
- Patient ID card, CEM manual, code panel – helpful elements.
- Data analysis is one from the critical stage; high professional level, clinical experience in ARVT safety-efficacy monitoring and professional motivation for clinical advisor is essential.
CEM in Belarus. **Partners and investigational team**

- **MOH:** Dr. Zhilevich Liudmila, Head of the Department of primary care of the MOH of RB
- **WHO:** Dr. Shanthi Pal, WHO country office –Dr. Iliencova Vera
- **UMC:** Dr. Sten Olsson, Dr. Geraldine Hill, Mrs. Monica Ploen
- **GFATM** Grants Implementation Unit UNDP Belarus and mission of PROON and UNAIDS in Republic of Belarus (Dr. Dubovik Oleg)

**HCPs:**
- Minsk: Dr. Dzmitry Paduto (Focal person, HIV coordinator), Dr. Natalia Rossa, Dr. Anna Kutuzova
- Gomel, Svetlogorsk: Dr. Elena Kaznacheeva, Dr. Elena Kozarez
- Shlobin: Dr. Elena Dodaleva
- Soligorsk: Dr. Marina Vecherka Dolbik, Dr. Svetlana Bondar

- **Clinical Supervisor:** Prof. Dotsenko Marina

- **National pharmacovigilance center:** Dr. Alla Kuchko (Field Coordinator), Dr. Setkina Svetlana (CEM coordinator), Dr. Iryna Charnysh (CEM Administrator)
Active surveillance – extremely effective way for extensive covering of the specific safety knowledge gap, have unique results-expenses ratio. For the best result very important to have high professional, well trained and motivated team with an appropriate resources.
THANK YOU VERY MUCH FOR YOUR ATTENTION!

QUESTIONS....