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Ph. D. Thesis

EPIDEMIOLOGICAL CONSIDERATIONS ON HIV INFECTION IN CONSTANȚA COUNTY

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KEY WORDS:

HIV-AIDS infection

Epidemiological considerations

Natural history

Constanța County

INTRODUCTION

The global AIDS epidemic is one of the greatest challenges facing our generation. AIDS is a new type of global emergency-an unprecedented threat to human development requiring sustained action and commitment over the long time. **[2004 Report on the global AIDS epidemic, Preface, Kofi A. Annan, http://data.unaids.org/Global-Reports/Bangkok-2004/Unaidsbangkokpress/gar2004 html/GAR2004_01_en.htm#TopOfPage]**

In many parts of the world, HIV/AIDS is still seen as a death sentence, a disease from which there is no recovery. But with the ever improving availability of antiretroviral therapy, HIV is increasingly recognized as a chronic rather than terminal illness. This transition requires special adjustments especially in the pediatric and adolescent populations. **[HIV Curriculum for the Health Professional, Kristin L. Close, Andrea K. Rigamonti, Psychosocial Aspects of HIV/AIDS: Children & Adolescents, p.296, http://aidsdatahub.org/dmdocuments/Psychosocial_Aspects_of_HIVAIDS_Children_ &_Adolescents.pdf.pdf]**

The epidemiological trend of evolution of HIV-AIDS is a topic of great interest to the scientific community today.

The discovery impact of HIV cases in 1990, with an explosive increase in the number of HIV confirmed cases, without being able to deepen the epidemiologically phenomenon and the lack of accurate explanations on the emergence, development and subsequent evolution of the epidemiological phenomenon caused were determinants on the choosing of the theme.

We proposed to organize the existing case registrations in a database that represents a prerequisite for further steps to elucidate the epidemiological process.

We monitored the factors that favored the dissemination of infection, unable to specify who the sources were.

KNOWLEDGE

AIDS was first recognized in Romania in 1985. **[1]** Until December 1989 a number of 10 AIDS cases were reported to WHO. From June to December 1989 a number of blood specimens from hospitalized children were found to be HIV positive. Further investigations and HIV testing were prohibited. From January 1990 reports of large number of children with AIDS began to emerge. The new Ministry of Health, with the support of WHO experts, CDC, epidemiologists and international NGOs, implemented a Short Term Plan of Actions. Factors contributing to the HIV epidemic in Romania:

- the social and economic policies of the former government resulted in increased numbers of malnourished, abandoned children

- the general public was not informed on the existence of AIDS in Romania and poor information was available on the ways by which HIV can be transmitted, or on the means that can be used for protection against the infection – besides, contraception was totally forbidden
- blood transfusion was not systematically screened for HIV infection; no laboratory equipments for blood testing was available in the 43 blood centers of the country
- broad indications for transfusions, with frequent transfusion of small amount of unscreened blood or plasma to sick or malnourished infants, was also important
- a severe shortage of medical supplies, as drugs, injection equipment and the lack of or inadequate sterilization or disinfection practices likely resulted in HIV spreading of infection of many infants
- a generalized use of therapies involving injections as of consequence of the lack of oral therapies was wide spreading
- the general hygiene in hospitals and in orphanages was deficient due to almost systematical lack of disinfectants
- the insufficient number of the health care workers and their poorly training
- the absence of implication of the services for social assistance or for health education
- finally, practices like commercial sex, MSM and the use of drugs, not allowing to know the spread of HIV infection among them.

AIDS Cases Surveillance started in Romania from April 1990, Sentinel HIV Surveillance System from April 1990, Blood screening in whole country from October 1990, anonymous voluntary testing from April 1990 and special studies like Screening of all institutionalized children in 1990 and Screening survey of pregnant women from eastern districts of the country in 1990.

After January 1, 1990, in Romania, a National Programme on AIDS was set up, with the support of WHO. Within this Programme, a national AIDS cases were registered in Romania (6, 2 cases/100.000 population). Of the total reported cases, 80, 2% were diagnosed after January 1990. Significant number of cases was registered in the eastern and southern part of the country. Constanța district have reported 36, 8% of the total cases.

Looking for the risk factors it is possible to describe 2 presumably patterns:
- Constanța – the peak of infected children is in 1988, cases with documented infective blood transfusions, suspected secondary spreading in medical settings
- Romania (without Constanța) – the peak of infected children is in 1989, transmission through the improper use of needles and syringes strongly suspected, no documented infective blood transfusion. **[1]**

The incidence of multiple injections for the children with AIDS born after 1st January 1990 had decreased 75, 2 times. The incidence of the multiple hospitalizations for children

with AIDS born after 1st January 1990 decreased 5, 8 times. The incidence of transfusions for children with AIDS born after 1st January 1990 had decreased 2, 4 times. **[2]**

The objective of the study release in 1992 was to describe the epidemiologic and clinical features between 2 month and 5 years old of 650 cases of pediatric AIDS identified in Constanța, district in Romania, since September 1989. Poorly sterilized equipment can clearly be responsible for the spread of HIV. Main route of transmission was through blood transfusions so in future great HIV problems will be in adults**. [3]**

The objective of the study release in 1994 was to observe the neurological manifestations in HIV infected AIDS children. We have retrospectively reviewed our cohort of 600 children with HIV infection AIDS from Constanța, ages 2 months to 7 years. We use clinical study, neurological exam, head circumference, the DENVER test, the cerebrospinal fluid (CSF) exam, computed tomography (CT) and neuropathology findings. Neurological manifestations: progressive encephalopathy 15%, static encephalopathy 40%, scizures 40%, TB meningoencephalitis (8 cases), bacterial or fungal meningitis, acute aseptic meningitis. CSF findings: lymphocytes pleocytosis and elevation of protein, detection of HIV1 core antigen and synthesis of HIV1 specific antibodies. Cerebral atrophy, microcephalies were detected by CT scanning or postmortem. Central nervous system involvement in HIV infected children is a frequent and heterogeneous manifestation. **[4]**

During 1990 - 1994, a number of studies shows that Romania, for the time being, the HIV epidemic recognize an epidemiological pattern quite different from all other described ways of evolution. The characteristics of the pattern are: the great number (90%) of HIV-AIDS of recorded cases are children less than 12 years old; in the investigated aria, HIV infection is revealed only in children up to 5, born to seronegative mothers and nursed in orphanages. Usual measures of hygiene, decontamination and asepsis, control of blood donations, reduction of transfusions and of parental medical practices seceded in interruption of resurgence of new cases of HIV infection in the observed children settings. **[5]**

România, a South Eastern European country with over 22 milion inhabitants has over 50% of the total HIV infected children or adolescents in Europe.

On 01.09.2004 there are 600 HIV infected children or adolescents alive in Constanța, of which about 200 are orphaned or abandoned and live in family type houses. The main current problems related to HIV- AIDS in Constanța County, as well as in Romania, are the following: the great majority of the children or adolescent , 95%, are between 16 – 18 years old and will soon begin their sexual life, the information about HIV and the sexual education among the young people being very poor in Romania, the preparation and the possibility that the HIV infected young people have an independent life are almost inexistent, their future uncertain although they are ensured with the antiretroviral treatment. **[6]**

An observational study of the department of pediatrics in Constanta County Hospital, performed on 153 HIV-infected patients in the period 1990-2002, with a comprehensive analysis extended to 2008, with the majority of children (144 cases, 94.11%) born between 1987 - 1989, of which many were born in 1988 (62.75%) demonstrates how transmission through unscreened blood transfusion and other medical practices , like incorrectly sterilized injection equipment in 32.67% cases and 48.36% cases with nosocomial transmission. **[7]**

Romania is one of the countries of South-east Europe where most HIV infections are HIV-1. Nowadays, in Eastern Europe, are only a few studies documenting the natural history of HIV-1 infection.

Context of the research: Constanța - tourist city with special profile (port, airport)

- Industry (Petrochemical - Midia Năvodari), agriculture (state farms, agricultural production cooperatives), geopolitical conditions, prior to 1989

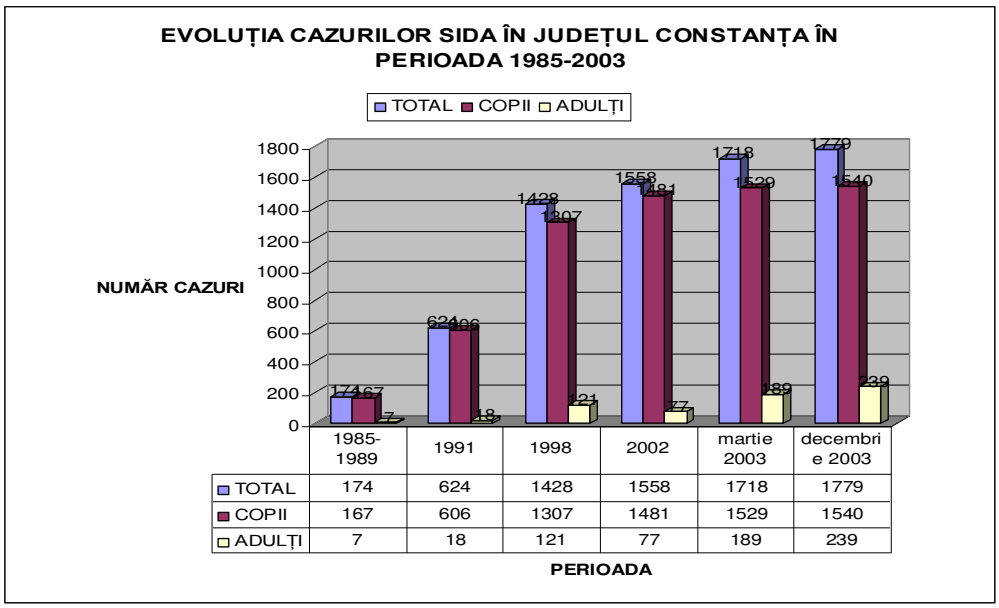
- Population coming from other counties (Moldova) for a job (housing and coastal construction, the canal Danube - Black Sea, the port expansion)

- Population and professions at risk (sailors, airmen, sex workers, inmates)

- the increase of the number of children admitted to pediatric wards, from families unorganized or abandoned children.

The evolution of AIDS cases in Constanta County during 1985-2003 shows a rapid upward curve detections in children in the first decade, the low rate of screening in adults in the first decade with absolute predominance of cases in children and increased progressively slower the number of cases identified in the second decade, on account of the increase in the number of cases in adults.

Figure 1. Evolution of AIDS cases in Constanta County, during 1985 – 2003



MATERIAL AND METHODS

Lack of available epidemiological studies and circulation of unverified and unsubstantiated scientific information contributed to the uncertainty regarding the onset, causes and epidemiological developments in Romania.

We made an analysis of the course of HIV infection in Constanta for the period 1987-2013. The patients were investigated through epidemiological surveys, clinical examinations, and laboratory and immunological. For statistical analysis we used Microsoft Excel.

This paper aims to formulate bioethical and epidemiological considerations on the evolution of HIV infection based on a retrospective and prospective epidemiological analysis of determined groups of patients from Constanța.

We established three groups of patients:

1. Registered in the period 1987-1993, which is mainly cohort of children infected through nosocomial transmission - included in Study I, retrospective.

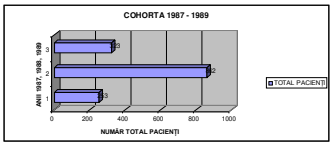
2. Registered in the period 2008 - 2012 - included in Study II, prospective

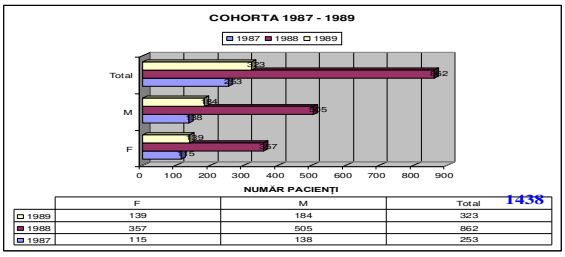
3. Registered in the period January-30 June 2013 - included in Study III, prospective, which aims to create a follow-up in terms of other ways to develop rigorous epidemiological investigation, to implement the necessary measures to optimize future prevention.

Figure 2. Groups of patients

LOTUL A

COHORTA 1987 - 1989



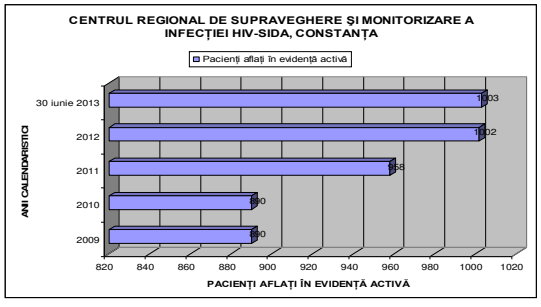


	F	M	Total
1989	139	184	323
1988	357	505	862
1987	115	138	253

1438

Analiză epidemiologică retrospectivă	Caracteristicile cohortei 1987-1990
VÂRSTĂ	TÂNĂRĂ: COPII 3 – 5 ani
GEN	MASCULIN
STRUCTURĂ	- asemănătoare cu datele la nivel național.

LOTUL B (2008 - 2013) conține 2 segmente: cohorta pacienților infectați în 1987-1989 (supraviețuitori de lungă durată) și pacienții infectați pe celelalte căi (heterosexual, IDU, MSM, MTCT)



VÂRSTĂ	ADOLESCENȚI ADULȚI
GEN	MASCULIN

The first epidemiological study is focusing on the characterization of the retrospective cohort from Constanța, which is presenting in archived database from 1987 to 1993.

The second study presents contributions on epidemiological description of HIV infection in Constanța County during the period 2008-2012.

The third study presents updated contributions on the prospective epidemiological description of HIV infection in Constanța County during the period January-30 June 2013.

Epidemiological considerations are made on the comparative study of the evolution of the cohort during the various chronological periods.

We conducted a study on two groups of patients selected from the cohort from 1987 to 1989, based on 2 distinct patterns of evolution: acute (from 1987 to 1993, retrospective study) and chronic course (2008-30 June 2013, study prospective).

We formed two cohorts, analyzed in 3 studies.

Group A (acute evolution - from 1987 to 1989 cohort, representing the natural history of the disease), with a survival rate of 18-24 months initially, then 4-5 years, who received only palliative care and medical assistance, with causes of death opportunistic infections and high mortality. The orphan patients were from dystrophic and premature wards and mostly were being institutionalized or abandoned children.

Group B - contains two segments: the 1987-1989 cohort of infected patients and patients infected by other routes heterosexual, IDU, MSM , MTCT), with the chronic evolution between 2008 - June 30, 2013, is consisting of patients undergoing antiretroviral therapy 10-11 years (2008), in the records of 12-13 (2008)-18 years (2013), both derived from cohort and newly detected, lasting average survival of 10 to 11 years, reduced mortality , predominantly through TB or pneumocystosis in poliexperimented patients, exhausted immunological or non-adherent status.

There are long-term survivors (slow progressors and non- progressors), which completes, part of them, the natural history of the first group, provided that not need treatment, because less influenced immunological status.

There are four models of evolution:

Lot A - acute and over- acute evolving - fast progressors (mortality rate increased, with duration of survival of 4-5 years), group B - chronic evolution - late presenters, slow progressors, non- progressors - the 3 new " patterns " are correlating with an increase in average life expectancy at 10.5-11 years, due to, in the overwhelming majority, the therapy and the natural history).

We estimate an evolution of the HIV AIDS epidemic in Constanta Count, on an average of 7-9 years, in the same parameters, which were characterized by the current study.

The main objective of this paper is to formulate bioethical and epidemiological considerations of HIV - AIDS in Constanta County, by describing the epidemiological characteristics of HIV - AIDS from Constanta county, HIV- AIDS epidemiological model locally.

Study I - Contribution to the epidemiological characterization of the retrospective cohort from Constanta

The cohort of children born in the period 1987-1989, which was individualized in Constanta, can be characterized retrospectively from epidemiologically and clinically, in a period (1987-1993). Since in the period under review there were no specific therapeutic means (antiretroviral therapy), results will highlight the natural history of HIV - AIDS in the study area (Dobrogea) .

Main Objective – Epidemiological considerations on HIV infection in Constanța County**,** during 1987-1993.

Secondary objectives:

1. Description of the epidemiology of HIV-AIDS from Constanta County during 1987-1993.
2. The local epidemiological model (1987-1993)

Materials and methods - Processing the existing database, records of the consultations, surveys on assessing health status, pathological, laboratory data, clinical observation on multicriterial sheets, the register of deaths and pathological examinations.

In Constanta we have the cohort of children born in the period 1987-1989, as part of the national cohort, the largest in Europe at the moment of 1990.

In this study we have a complex epidemiological investigation of cohort during 1987-1993, an opportunity to study the natural history of a disease, by characterizing the newly identified population at risk of acquiring the disease, from the first moment to the moment of first initiation on therapeutic means.

A database, recorded during 1987-1993, was analyzed. Were first studied 1728 HIV-AIDS cases detected in Constanța.

The vast majority of the population in cohort comes from public care and pediatric wards, dystrophic, premature, infant surgery of Constanta County Hospital.

Organization and data collection was performed, through analysis in terms of ordering data, correlation, and validation: descriptive analysis of the elements which determine the distribution of cases. We have identified characteristics from **[8]:**

1. Time - tendency , variation , the distribution of the disease by the time variable (changing age structure over time)
2. Place - geographic (latitude, longitude - Black Sea port, airport, tourist city, ways of introducing in the country: people on the move, traveling. We made the

evaluation of HIV - AIDS on geographical level emphasizing geographical distribution, population at risk, prioritizing risk factors, for geographical comparisons we used cartograms), geological, industrial (petrochemical-Midia Năvodari), agriculture (IAS, CAP), climatic, geopolitical conditions, prior to 1989, blood products, pollution status, place of work (childcare institutions, sex workers, accidental exposure)

3. are evaluated the determinants of public health problems, are shown to define the characteristics of the affected population, the risk population - variable 'person' (belonging to a group of high - risk, the health providers, travelers, isolated populations, who might - by changing life behavior - to be at risk of infection. Aspects of demography - biological epidemiological indicators like gender / sex [M, F], age [age group, adult - children], ethnicity, race, area of origin [U , R], village of origin, place of residence, behaviors [donor blood, MSM, heterosexual, IDU, sex workers], profession, occupation, life style, socio-economic level, and other information - migration, tourism) **[8]**

We proposed to observe, to describe cumulative, the explanation of the phenomenon, to monitor, to control (preventive measures, and curative - ARV) and to formulate the considerations based epidemiological verified. We conducted descriptive analysis for categorical data (frequency, percentage) and quantitative (average - homogeneous nature of the cohort, i.e.: median, range, standard deviation, heterogeneous character of the lot). Collection of raw data was ordered and grouped in tables and charts, on chronological criterion. I used tables for their economic character, the most simple and effective explanation of the evidence, because we wanted to present a large number of data. Herds were expressed in distributions, frequency distributions

Study II - Contributions to the epidemiological characterization of prospective description of HIV in the Constanta County, during five years tracking (2008 - 2012).

We proposed, compared with the group that was the subject of the first study, to collect data, general epidemiological aspects, such as HIV - Aids's progression in the county, number children infected with HIV - AIDS, clinical- biological evolution imposed by the monitoring of ARV treatment, which is mature.

The introduction of HAART has increased the survival of patients and changed the pattern of mortality, with complications resulting from ART - lipodystrophy , increased incidence of cardiovascular disease , organ failure , resistance to ART, ART discontinuity in nonresponder, lack of compliance and adherence , cases of contracture Dupuytren, tenosynovitis, arthritis temporomandibular post indinavir, the lipomatosis of the parotid associated with IP .

The group of patients in the period 2008-2012 is constituted both from children born during 1987-1989 (the original cohort) - long-term survivors and from patients infected by another route (MSM, MTCT, IDU).

Main Objective - Epidemiological considerations on HIV infection in Constanța County**,** during 2008-2012.

Secondary objectives:

1. Description of the epidemiology of HIV-AIDS from Constanta County during 2008-2012.
2. The local epidemiological model (2008-2012)
3. Epidemiological investigation by 1 day.

Study III - Contributions to the epidemiological characterization on prospective description of HIV in the Constanța County, during 6 months (January - 30 June 2013, study-pilot).

Based on epidemiological and historical context for the first 6 months of 2013, we implemented an active surveillance epidemiological model, with correlation of all factors, including new and old cases. Study III is a model -based tracking active epidemiological data, reporting monthly, quarterly and corroborating of the clinical efficiency indicators with official's indicators, which required to be reported.

Main objective - Epidemiological Considerations of HIV in Constanta County, during 6 months follow-up (January - 30 June 2013, pilot study).

Secondary objectives:

1. The epidemiological description of HIV - AIDS in Constanta County, during January- June 30, 2013
2. The epidemiological model of the period.

RESULTS AND DISCUSSION

First Study - Phase conclusions :

1. During 1987 to 1990 there was an uninformed population on HIV- AIDS phenomenon, which later will become familiar with the existence of infection, transmission patterns and healthcare opportunities (after 1990).
2. Since at that time exist not etiological treatment, all patients in the studied group received comprehensive medical care, including improved care, which have been applied in both hospital and ambulatory, until death. The clinical course of this group represents a segment of the natural history of HIV - AIDS in Constanta County.
3. The route of transmission was: transfusion, injections (parenteral, 84.549 %). The treatments were performed in pediatric wards (Pediatrics I - N = 78, 4.514 % and Pediatrics II

- N = 337, 19.502, accumulating a total of N = 415, 24.016 %), and the parenteral treatments in other sections (dystrophic, premature baby, swings).

4. The discharge diagnoses for children were: atrepsy (N = 74, 4.282 %), dystrophy (N = 174, 10.069 %), MPC (N = 24, 1.389 %), severe weakness syndrome (N = 148, 8565 %). Co-infections HIV-HVB/HVC is explained by simultaneous transmission (same route of transmission).

5. Orphan patients came from wards dystrophic and premature, mostly being institutionalized or abandoned children.

6. The epidemic was characterized as follows: rural type (N = 635, 36.748 %) , which , together with the percentage of the institutionalized children (14.12 %) , forming about 51 % (50.868 %), the rest being found in urban (49.132 %). After 1989, rural- urban social mobility is an explanation of urbanization trend, which persists in 1990, 1991 and 1992, with a better detection of infection in city.

7. In the studied cohort, pediatric population prevails, within it a number of N = 21, 1,215 %, from multiple pregnancies (twins, trigemelare).

8. The determinant virus is “wild”, new in circulation, with no immunity in the population.

9. There was an epidemic, due to the number of cases diagnosed within a very short time.

10. The evolution of the epidemic had imposed unprecedented organizational measures of health services, to ensure optimal support of a large number of cases (creation of additional space for pediatric population near Constanta Municipal Hospital, where they were brought all HIV-positive children from orphanage, to ensure their uniform assistance).

11. The diagnosis of the cases in this period was mainly clinical and initially reduced only to HIV testing by ELISA, then gradually was expanded the scope of biological investigation, trying to standardize them.

12 Was an initial high mortality, which best defines the “pattern “of development of infection in the study group (rapid and profound impairment of the immune system with rapid deterioration and death).

13. HIV can be a model for monitoring other chronic infections (oncology, hematology, hepatology).

The originality of this study is to update the incipient data base with extremely valuable data, unused entirely from the perspective of the epidemiological phenomenon.

Second Study - Phase conclusions

1. In the period 2008-2012 the population is familiar with HIV- AIDS phenomenon, relatively informed about the risks of contracting the disease , outlining a new profile of the

patient, which is not seen in other specialties : patient aware of his own guilt, which had left his entire destiny in the hands of the physician , coming with hope and valuing life , which creates a special unconditional relationship between patient and physician (trust, humanity, persuasion) .

2. This new type of relationship is based on applying a modern therapies in terms of the increasing of the adherence and compliance, with the desire to live, in contrast to long - survival patients , exposed to all therapeutic schemes, on their penetration in the country (poliexperimented patients), whose desire to survive is declining and with cognitive impairment over time .

Appears the "therapeutic fatigue" with therapeutic vacations, There are repeated treatment interruptions, the negative impact on disease control. Many patients are in treatment failure. This attitude was determined by modifying the "pattern" of the disease, which has become a chronic condition, with an impressive decline in the death rate after the introduction of protease inhibitors (1996), creating the illusion that we can live without therapy.

The existence of therapeutic drugs, biological control (resistance tests, viral load, CD4) had involved a correct application of the guidelines through indicators: efficiency versus treatment failure, adherence and compliance, regimen used (over 3 drug combination is an art requiring knowledge of pharmacogenomics), hospitalized patients , with non-adherent status (treatment failure), mortality (much reduced level on cohort, but increased value to those who reach the hospital, affected by lack of response) **[Sebastian Wanless , Reporting and Standards Medical EMC , September 18, 2009 , BIPAI , The International School "Best Practices in the Care of HIV-Infected adolescents and Youth " , September 1-4 , 2008 , Constanta , Richard Sebastian Wanless " M & E indicators - May 2008. BIPAI's clinical outcomes in Africa as a demonstration of how effective can be HAART programs for children in resource- limited settings "]**

This system of tracking the indicators was a priority, constantly being applied to network centers of excellence BIPAI.

The monitoring of the CD4 level and use of prevention guidelines had involved the prophylaxis of the co-infections (hydrazine for TB, clarithromycin for mycoplasma, cotrimoxazole for pneumocystosis), which has complicated the clinical pharmacology of these ill, with impact on evolution of complications, on short-term effects (toxic) and on long-term effects (metabolic, lipodystrophy, neurocognitive) .

3. The route of transmission is predominantly heterosexual, with a significant increase in patients MSM and with IDU transmission. There are difficulties of diagnosis in women of childbearing age with birth years 1987 - 1989, detected during this period, which is difficult to affirm that are part of the cohort (nosocomial transmission) after starting sexual life, with problems genotyping. Genetic methods would be required to make the etiology of the cases and give a verdict on the precise epidemiological transmission. Appear patients from families with HIV clusters.

4. The discharge diagnoses are with prevalent co-infections , in which there is a significant increase in HIV -TB co-infections , with the occurrence of pulmonary form with multidrug-resistant to drugs, with fatal respiratory failure , death with neurological impairment, especially tumors , cirrhosis and hepatocellular carcinoma in coinfections B. The NeuroAids pathology is important - the specialists' clinicians faced with complex neurological manifestations: distal sensory polyneuropathy, inflammatory demyelization polyneuropathy, poliradiculopathy, progressive neuromuscular weakness syndrome, and progressive multifocal leukoencephalopathy, encephalitis, demyelization lesions, which generated needs further investigation and support (NeuroAIDS National Project). TB was the cause of the aggravation and the most common cause of death diagnosis, intravital or postmortem. With a National Programme for Prevention and Control of TB, with inadequate functionality, TB incidence has increased, predominantly in males.

In the study group during 2008 - 2012, HIV- AIDS pathology becomes more complex by affecting kidney: renal disease, ITU, lipodystrophy, ITS - hematological anemia, thrombocytopenia, leucopenia, lymphocytopenia, neutropenia, pancytopenia, diseases of the liver (elevated transaminases, associated with the energy - drink consumption behavior), diseases of the skin (Norwegian scabies, Kaposi syndrome).

The maternal- fetal transmission is a segment of the prevention and control of HIV, well structured, with good control, with small deviations related to the level of culture of patients and with healthcare rigorous functionality, but not excluded birth of premature babies with malformations.

5. Patients are cared for primarily in family -friendly environment in all aspects: environment, help, human and material support, and therapeutic discipline.

6. Epidemic is an urban epidemic, with new cases detected with heterosexual transmission route and newly diagnosed patients with late presentation (late - presenters).

7. There are long-term survivors (slow progressors and non- progressors), which completes one part of the natural history of the first batch, with no need of the treatment, because the immunological status was less influenced. There are 4 patterns of evolution: acute and over-acute (rapid progressors, the mortality rate increased with duration of survival of 4-5 years) and those with chronic evolution (late-presenters, slow progressors and non- progressors - these 3 " patterns " correlate with an increase in average life expectancy at 10.5-11 years, due, in the overwhelming majority, therapy, and, to some extent, due to natural history).

We have no data to objectified the differences in the natural history of evolution - there are complex factors that will be elucidate over time (molecular tests), but we mentioned the clinical and epidemiological development.

Hospitalized patients are noncompliant, are in treatment failure.

8. Because of the many therapies and complex combinations, because of the virus resistance mutations, leading to treatment failure and the exhaustion of treatment.

9. It is an established epidemic, based in particular on new methods of transmission, IDU, unprotected sex, changing psychological profile of young adults (exposure to risk factors - tattoos, piercing, ethno botanical, drugs, and casual sex).

10. The late-presenter assistance and those with worsening trend towards palliative care requires expansion means that acquires a special importance in completing care. History of HIV (and natural) involved the need for specialization and for differentiation the medical services. It established the Department of Palliative Care, which provides constant assistance. Now there are options (recovery palliative care with dying patients - "Lazarus Syndrome"). Current risk scores are established and evolving HIV- AIDS patients (EuroSIDA Risk Score: Risk of death or development of other AIDS-defining diseases : the next 3 months, 6 months, 12 months, Karnofsky score, BMI, SF -36 ...)

10. Problems related to adherence to treatment of the new patients, the need for mandatory counseling involved better clinical psychologist collaboration.

11 Medical care of patients in this cohort is becoming increasingly complex, using the most modern imaging methods in the investigation of neurocognitive syndrome, as well as pharmacogenetic and pharmacogenomic testing in managing therapy (determining HLA 5701 for abacavir, identifying delta 32 for certain categories of patients, therapeutic combinations with useful composition)

Third Study - Phase conclusions

1. In 2013 the population is well informed about HIV- AIDS phenomenon, relatively educated.

2. Those who are hospitalized are in the "stop ART" treatment failure due to" therapeutic fatigue".

3. The route of transmission remains heterosexual, but also like behavior MSM, IDU, partly MTCT (relaxation of the obstetric and gynecological supervision).

4. Discharge diagnoses are type NeuroAids, metabolic syndrome ... HBV co-infection is under control, using ARVs B virus (lamivudine , tenofovir ...)

5. Patients reached social maturity and they have their own families, they want to have their own children, which generally complicate epidemiological perspective of evolution.

6. The epidemic is urban type. More women hospitalized (N = 136, 57 143 %), compared to men (N = 102, 42.857 %).

7. It is a multi-resistant virus. The virus causes serious difficulties for doctors in the composition of potent drugs schemes.

8. It is an evolving epidemic, whose control requires time, is long lasting. Now is difficult to apply the “Directive 0" (Hilary Clinton).

9. HIV has led to a highly complex pathology, which called for the medical approach multidisciplinary teams.

10. The effective collaboration between psychologist and the clinician specialist had a positive impact on adherence control, had improved clinical outcomes for patients with hospitalizations.

11. Increased complexity of cases requiring complex biological investigations (latest serological methods to visualize the etiology).

12. The number of deaths is reduced; the principal is pulmonary pathology (lung tumors, pneumocystosis), tumors (tumors neurological, abdominal tumors), and major hepatic decompensation.

13. Although therapeutic advances were evident and appropriate therapy success, HIV patients continue to present problems of evaluation and monitoring.

14. The current approach of HIV represents a model for other chronic infections surveillance (oncology, hematology, hepatology)

In terms of statistical analysis, Bravais Pearson coefficient shows a good prediction.

Table I. Coefficients statistiques: Bravais Pearson

FIRST STUDY **Factors analyzed** **Period 1987 - 1989**	**r**	**p**	**CI**	**r_F**	**I**nterpretation
The number of births with the year of birth (cohort 1987-1989) and distribution of total pathological examinations during 1987-1993, according to the corresponding year of birth (1987, 1988 and 1989)	r=0,98302 n=2 (degree of freedom) The parametric coefficient of the correlation (Bravais Pearson) by the moment of the products (equivalent)	0.01	99% **Confi dence Interval**	r_F =0,99144> r Reliability coefficient of the test, method split half	Correlation coefficient is very tight, strong, positive, direct, those two factors vary simultaneously, the "cloud of the points" is oriented to the right. Place bisector I is approximated almost 45 gr. in quadrant I.

Table II. Risk factors / disease

Risk factors / disease	**HIV +**	**HIV -**	**Total**
FR +	**1696**	**17**	**1713**
FR -	**32**	**8**	**40**
Total	**1728**	**25**	**1753**

OR = 99.76471 exposed, unexposed OR = 4, OR = 24.94118> 1

Table III. Statistics: Bravais Pearson

Factors analyzed	**Period**	**The parametric coefficient of the correlation (Bravais Pearson) by the moment of the products (equivalent)**	**p**	**Confidenc e Interval**	**Reliability coefficient of the test, method split half**	**Interpretation**
Total number of pregnant women and the number of pregnant women receiving ARV prophylaxis 2008 -	2008 - 2010	r=0,96882 n=2	0.01	99%	r_F =0,98416> r	Correlation coefficient is very tight, strong, positive, direct, those two factors vary simultaneously, the "cloud of the points" is oriented to the right. Place

2010						bisector I is approximated almost 45 gr. in quadrant I.
The number of patients who received prophylaxis for TB and the number of patients diagnosed with confirmed TB 2008 - 2011	2008 - 2011	r=0,22762 n=3 The regression right tends to be parallel to abcisa.	0.10	90%	r_F =0,37398> r	Correlation is not very strong
Number of psychological tests	2008 - 2011	r=0,88 n=3	0.05	95%	r_F =0,93617> r	Correlation is very tight, strong

Table IV. Coefficients statistics: chi ^{2,} phi

Factors analyzed	**Period**	**Test chi ^{2}**	**p**	**CI**	**Coef ϕ**	**Interpretation**
Patients on ARV and patients without ARV in 2008 compared with the period 2008-2011	2008 and 2008 - 2011	**chi ^{2}** = 272,1942 n=1 probability = 0.000	0.01	99%	**ϕ** =0,19 - Φ correlation coefficient test based on chi 2	The relationship between variables is statistically significant, but not strong - low correlation coefficient ϕ.
Acute and chronic patients in rural and urban	2008 - 2012	**chi ^{2}** = 29,29072 n=1 probability = 0.000	0.01	99%	**ϕ** =0,0939148	
Patients on ARV	2008 - 2011	**chi ^{2}** = 101,5909 n=1 probability = 0.000	0.01	99%	**ϕ** =0,1624807	
Patients on ARV treatment and patients without ARV treatment compared with number of psychological counselors		**chi ^{2}** = 183,60059 n=1 probability = 0.000	0.01	99%	**ϕ** =0,18	

Deaths in 24 hours, in 48 hours, in 72 hours period 1987-1993 compared with 2009-2012	1987 – 1993 and 2009 - 2012	**chi ^{2}** = 25,00 n=3 probability= 0.00	0.01	99%	The relationship between variables is statistically significant.

The limits of the studies - First study made only retrospectively, describing the evolution of disease under existing data in the database. The HIV database was created through a lengthy process and during the period studied there is lack of information, so that affected the complexity of analysis, it not obtained data extremely accurate, enabling very valid epidemiological considerations.

The studies have their limitations, they could deepen epidemiological investigations in the light of modern molecular diagnostics, allowing generation of parentage cases, but have their own importance to this point in the investigation, paving the way for future research, that will elucidate correctly the epidemiological natural history of HIV infection in our country and will give the expected response of thousands of parents of deceased children.

The low number of the patients, in the third study, prevents formal conclusions. These results should be strengthened by analyzing a larger number of patients, frequency distribution, which requires further research started.

The limitations of the study are in the fact that can not yet elucidate the overwhelming presence of the F subtype in Romania in general, "an island in a sea of B subtype", and specially in Constanta, that shows a possible infection through " single source "which contradicts the route of transmission by transfusion, which was presented by the existing epidemiological surveys, approved at this time. The epidemiogen potential of F1 strain is important , given the large number of cases and the epidemic character .The import infection remains undervalued, as demonstrated phylogenetic relationship between strains HIV1 subtype F1, isolated in Angola and Romania, presented by Paraschiv S, Steel D. - "HIV - 1subtypes and resistance in Romania" on 2 - 4 September 2010 at the International School" HIV Medicine 2010' edition - II, Constanta, Hotel Ibis, organized by Baylor College of Medicine, Texas Children's Hospital, University Ovidius University Carol Davila Bucharest, citing the study" Close phylogenetic relationship between Angolan and Romanian HIV-1 subtype F1 isolates", authors: Monick L Guimaraes, Ana Carolina P Vicente, Koko Otsuki, Rosa Ferreira, FC da Silva, Moises Francisco, Filomena Gomes da Silva, Ducelina Serrano, Mariza G Morgado, Gonzalo Bello.

Subsequent epidemiological studies may explain this particular distribution, demonstrating the need to develop in-depth epidemiological studies.

Contributions - the originality of this study is to update the data base from early period, with extremely valuable data, entirely untapped in terms of epidemiological analysis of the phenomenon. This paper brings original features that allow completion of some major research areas, important for understanding the epidemiological characteristics of HIV in Constanta. The originality of the study: a descriptive presentation from the registers and studied observation sheets were transformed into a database, which was presented in the 3 studies.

CONCLUSIONS

1. During 1987 to 1990 there was an uninformed population on HIV- AIDS phenomenon, which later will become familiar with the existence of infection, transmission patterns and healthcare opportunities (after 1990).
2. The route of transmission was: transfusion, injections (parenteral, 84.549 %). The treatments were performed in pediatric wards, and the parenteral treatments in other sections (dystrophic, premature baby, swings)
3. Orphan patients came from wards dystrophic and premature, mostly being institutionalized or abandoned children.
4. The epidemic was first rural and subsequent urban epidemic.

5. Analyzing the pyramid of the ages, first time pediatric population prevails, subsequent adult population.

6. The determinant virus is "wild", new in circulation, belonging to subtype F1 overwhelmingly (99.9%).

7. The diagnosis of the cases evolved from clinical diagnosis and HIV testing by ELISA, by modern means of today (phenotype, genotyping, imaging, resistance tests).

8. Mortality rate fell spectacular, especially due to the introduction of antiretroviral therapy.

9. HIV can be a model for monitoring other chronic infections (oncology, hematology, hepatology).

10. - The special epidemiological situation described in the Constanta determined the catalyzed efforts to ensure an optimal assistance to HIV patients, achieving a number of "firsts" for the health system in Romania:

- Implementing the first center of care in family homes and palliative care;
- The first center of public-private partnership with Baylor, which was considered in the European Report as a "model of integrated cares by providing primary and specialized services, which evolve with the age of the assisted patients"(page 10, ECDC Report, Romania Country Visit, Marita van de Laar et all.)
- Modernization of the premises daily clinical care, continuous hospitalization, the section of chronicle patients - all included in an international grant sponsored by the European Academy of HIV-AIDS and Infectious Diseases **[9]**, with unbundled services on Pneumology, gynecology, dentistry;
- Model replicated through a network of excellence BIPAI in Africa, too;
- Methodological forum with health delegations of Uzbekistan, Turkmenistan, Tajikistan, Kyrgyzstan and Kazakhstan, Moldova, Ukraine and Byelorussia.

These results generate special concern in future epidemiological studies in depth to give the actual size of the phenomenon of HIV - AIDS in Constanta, and in Romania.

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