UNIVERSITY OF MEDICINE AND PHARMACY IN CRAIOVA

Mucocutaneous Diseases in HIV Type 1 Horizontally Infected Children between 1988 - 1990 - a Dermatoepidemiological Approach (1990-2007)

Abstract of Ph. D. Thesis

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Background and the Reasons for Choosing the Subject of the Thesis

In the case of the HIV/AIDS infection, Romania holds, in the history of medicine and infectious diseases, a unique place in the world due to the dominant category of patients and the way of acquisition of the infection with the human immunodeficiency virus (HIV): thousands of children born between 1988 and 1990 from HIV serum negative mothers were horizontally infected after birth, most of them during hospitalizations and accommodation in orphanages, via HIV-contaminated medico-surgical disposals, blood and blood derivatives.

The experience accumulated by the Romanian specialists in the management of this category of patients is remarkable and, in order to avoid future worldwide dramatic situations of this kind and to offer a fellow-like support in the comprehensive care of such cases, I consider that it is a professional and moral duty of the medical staff in Romania to turn to good account this experience in solid scientific paperwork and synthesis.

The dermatologic morbidity is probably the most frequent category of disease during the life of HIV infected persons; all of them will suffer at least one muco-cutaneous disorder in the course of the infection. Even though few muco-cutaneous diseases are directly associated with the progression of the HIV/AIDS infection or with the death of the patients, they represent a major health problem with negative impact on the quality of life, generating care problems and supplementary costs.

At the same time, a few of these diseases are considered as definitive conditions for AIDS (e.g. the Kaposi sarcoma and the herpes simplex chronic ulcer for more than 1 month) or heralds of the progression of the infection towards AIDS (e.g. oral hairy leucoplakia).
Thus, the identification and knowledge of the clinical-evolved particularities of the dermal-pathology of the HIV-infected persons could be a useful tool for the early detection of some cases and for the workout of the prognostic of an already known patient.

Clinical-evolved particularities, including dermatologic particularities, could emerge not only from the way and the moment of infection, but also from the etiology of the infection of these children - the subtype F of HIV-1 is found only among pediatric infected population in Romania and in some small communities in Africa and Brazil, and it is today accepted as being less aggressive than other subtypes.

An epidemiological-clinical approach of the dermatologic conditions of the HIV-infected persons offers a series of opportunities for the analysis and synthesis of specific data (and also the premise for transposing them in the practical management of cases):
- the visualization on a national level of an infectious relatively recent pandemic phenomenon, via a medical specialty, with the extraction and analysis of its specific problems;
- the dermatological approach of a group of patients in the Global HIV/AIDS phenomenon. These patients are practically combining the dermatologic diseases specific to the general pediatric local population and the muco-cutaneous conditions associated to the secondary chronic progressive immune suppression. The dermatological approach aims to identify the spectrum, incidence, prevalence and the specific conditions associated to each type of muco-cutaneous disorder;
- the possibility of establishing an hierarchy of the weight of the dermatological priorities in the comprehensive management of these type of HIV-infected patients, allowing for a more realistic construction of the proceedings of comprehensive care of these cases and the evaluation of the cost;
- the historic analysis of the way the dermatologic pathology of the HIV infected patients was practically addressed by the professionals involved in the primary care of these cases (infectionists and pediatricians) versus the dermatologists, with the designation of the limits of competence and of the necessities of an interdisciplinary co-operation;
- a more pragmatic and applied orientation in the dermatological training both theoretically and practically of the care providers of the HIV infected persons from various medical specialties and the dermatologist in the area of HIV/AIDS infection respectively.

**Aims and Objectives**

The aims and objectives of our scientific study were:
- the definition of the dermatologic phenomena in the course of the HIV/AIDS infection in horizontally HIV-infected children during 1988-1990
- the establishment of the spectrum, incidence and prevalence of each dermatologic condition as well as of the major etiological and clinical categories, in the different stages of evolution of the HIV infection and their
relationship with the antiretroviral therapy (TARV)
- the correlation of the muco-cutaneous diseases and the dermatologic morbid burden with the level of immune suppression, the nutrition status, the non-dermatologic associated co-morbidities
- the identification of some possible dermatologic profiles within this particular category of HIV-infected persons
- the definition of the place of the dermatologist in the multidisciplinary care team of the HIV infected persons.

**Material and Methods**

The study included HIV infected persons born and infected during 1988-1990, from the records of specialized centers in the diagnosis and monitoring of HIV infection in Craiova (the Clinical Hospital of Infectious Diseases and Pneumology “dr.V.Babeș”), Timișoara (the Clinical Pediatrics Hospital “L.Țurcanu”) and Bucharest (the National Institute for Infectious Disease “M.Balș”).

The study had a mixed character: retrospective for the period 1990-2004 and prospective for the period 2005-2007.

In order to achieve the dermatologic data base, I have analyzed the data mentioned in the primary records of the above mentioned centers.

The prospective study was based on the dedicated “dermatologic monitoring records of the HIV infected patients”, specifically conceived for each historic period of treatment of the HIV/AIDS infection (the pre-antiretroviral period, the therapeutic transition to cARV, and the combined ARV therapy: the post-HAART period).

I have calculated the incidence, the prevalence as well as the dermatologic morbid burden (DMB) for each group. In statistical analysis I used the standard descriptive statistic processing. The data were processed with EPI Info.6 from CDC.

In order to compare the data, I have used witness groups of HIV serum-negative children and adolescents of similar age, which were dermatological evaluated in the same period of time with those included in the study.

**Study Design**

The design of the project has included 3 sub-studies, corresponding to the historic type of therapeutic approach of the HIV infection in Romania:

a. the pre - ARV’s period (1990-1995) - during this period of time, the treatment consisted only in the prevention and therapy of the opportunistic conditions, alike with symptomatic, nutritional and psychological approach of the patients.

b. the beginnings of the ARV therapy (the “ARV transition”) between 1996 and 1999 - now is the time for the initiation of the ARV treatments, first as mono-therapy with AZT, then as bi-therapy with 2 nucleosidic inhibitors of the reverse transcriptase and, afterwards, with multiple associations of drugs from different classes (the HAART strategy). The efficiency of the mono- and bi-therapy is inferior to HAART and the therapeutic success is limited in time.
That is the reason why, during that period of time, the therapeutic impact on different HIV-associated disorders was unequal and shortly lived.

All types of treatment were present in different proportions in the same period of time among the patients in our group. That is why the individual successes could be statistically diluted. That is the reason why I considered as necessary a differentiated approach of this period.

c) the HAART and post-HAART period (2000-2007) is a complex one: we can observe the beneficial effects of these therapies on the morbidity and mortality but also the development of new pathologies related to this new medication (the long term toxic effects of the ARV drugs, the drugs interactions and even the immune restitution), all with impact on the mucocutaneous diseases.

I have elaborated a matrix of common approach for all the sub-studies (the analysis of the group including the spectrum, incidence and prevalence of the entities and major categories of mucocutaneous diseases, in multi-annual dynamics, DMB, factors of influence of the epidemiology of the dermatologic conditions: sex, age, level of immune suppression, nutritional status, non-dermatologic co-morbidities - compared to groups of HIV negative patients of similar age.

**A synthesis of the main results**

The main general characteristics of the subgroups are presented in the table no. I

**Table no I. General characteristics of the subgroups**

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Sub-study I</th>
<th>Sub-study II</th>
<th>Sub-study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of the study (years)</td>
<td>6</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>General group (no. of patients, cumulated)</td>
<td>804</td>
<td>673</td>
<td>1008</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>3,6 ± 2,1</td>
<td>8,5 ± 1</td>
<td>14,9 ± 2,4</td>
</tr>
<tr>
<td>Average age of the HIV infection (years)</td>
<td>3,5 ± 1,3</td>
<td>8,3 ± 0,8</td>
<td>14,2 ± 2,1</td>
</tr>
<tr>
<td>Female (%)</td>
<td>48,3 %</td>
<td>52,5 %</td>
<td>50,5 %</td>
</tr>
<tr>
<td>The immunologic category (CDC, 1994) initially (% Px)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 500 Ly CD4/mm³</td>
<td>32,5 ± 1,6</td>
<td>25,3 ±1,4</td>
<td>15 ± 2,8%</td>
</tr>
<tr>
<td>200-499 Ly CD4/mm³</td>
<td>33,9 ± 1,5</td>
<td>33,3 ± 2,3</td>
<td>33,6 ± 3,1</td>
</tr>
<tr>
<td>&lt;200 Ly CD4/mm³</td>
<td>34,4 ± 1,6</td>
<td>41,3 ± 2,2</td>
<td>51 ± 5,7%</td>
</tr>
<tr>
<td>The type of treatment of the HIV disease</td>
<td>Tx of opportunistic infections</td>
<td>ARV mono-, bi-, tri-therapy</td>
<td>cARVT (HAART)</td>
</tr>
</tbody>
</table>

IV
In the table no. II there have been synthesized some data of dermatologic epidemiology.

We can notice that the proportion of HIV infected patients with dermatologic diseases lowers in time (from 85% to 71%); the same phenomenon is observed in the case of the average yearly number of HIV-infected patients with muco-cutaneous disorders deceased during the study (simultaneously the average number of HIV infected patients without muco-cutaneous diseases alive at the end of the year, grows).

**Table no. II. Synopsis of general dermatologic data**

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Sub-study I</th>
<th>Sub-study II</th>
<th>Sub-study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dermatologic exams necessary for the inclusion in study (no. of cases cumulated)</td>
<td>≥1/year (489)</td>
<td>≥2/year (544)</td>
<td>≥ 4/year (685)</td>
</tr>
<tr>
<td>Patients with HIV without dermatologic conditions deceased (yearly average number)</td>
<td>3 ± 1,3/year</td>
<td>6,7 ± 2,1/year</td>
<td>5,9 ± 1,35/year</td>
</tr>
<tr>
<td>Patients with HIV infection without dermatologic conditions alive at the end of the year</td>
<td>9,3 ± 2,9/year</td>
<td>22 ± 1,8/year</td>
<td>157,9 ± 47,5/year</td>
</tr>
<tr>
<td>Patients with HIV infection with dermatologic conditions (nr. %)</td>
<td>415 (84, 9%)</td>
<td>429 (78, 7%)</td>
<td>487 (71, 1%)</td>
</tr>
<tr>
<td>Patients with HIV infection with dermatologic conditions deceased</td>
<td>12,7 ± 3/year</td>
<td>21,5 ± 4,8/year</td>
<td>10,3 ± 2,25/year</td>
</tr>
<tr>
<td>Patients with HIV infection alive at the end of the year</td>
<td>182 ± 11,3/year</td>
<td>328,3 ± 14,5/year</td>
<td>439,8 ± 19,2/year</td>
</tr>
<tr>
<td>Dermatologic entities-cumulated identification</td>
<td>53</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Dermatologic conditions-cumulated in years</td>
<td>914</td>
<td>1885</td>
<td>5835</td>
</tr>
<tr>
<td>Dermatologic conditions-the average/year</td>
<td>152,5 ± 40,1</td>
<td>471,25 ± 22,3</td>
<td>729 ±116,2</td>
</tr>
</tbody>
</table>

At the same time, the number of dermatologic entities identified grows with each sub-study. The grouping of these dermatologic entities in major categories of dermatologic conditions (infectious diseases, non-infectious diseases and miscellanea) allows for a better understanding of the data collected in each period and in relation with the type of treatment of the HIV infection.

If the dominant dermatologic conditions in the period of empiric and non-specific treatments were the infections (64.1%), with the introduction of the ARVT and the generalized use of strong, combined therapies, the proportion of the infections lowers significantly (54%). The reduction is due especially to the viral and parasitic cutaneous infections and also to the mucous diseases.
In the group of non-infectious diseases, the growth is due to the category of miscellanea disorders/hard to classify disorders, including some muco-cutaneous diseases related to the ARV therapy.

**Evolution of the Dermatologic Morbid Burden**

Overall, in the absence of the ARV therapy (sub-study I), even if we can identify a significant growth of the value of the DMB in time (from 1.66 in 1990 to 2.31 in 1995), the statistic significance is absent.

The growing trend of the DMB of the HIV patients without ARV therapy remains important.

During the period of therapeutic transition, the general average value remained stationary in time (4 years); we could speculate that, for some patients, the value lowered, for some patients it grew, and, due to the phenomenon of statistic dilution, the value remained close to the extremes of the study.

But the sub-study III showed that the combined ARVT in HIV infected patients with at least one therapeutic line failure, could be associated with a reduction of DMB value (1.96 in 2000 and 1.55 at the end of the study, in 2007), and the difference is statistically significant (RR 1.16, p = 0.01).

**Factors of Influence of the Value of the Dermatologic Morbid Burden**

The level of the immune suppression shows a negative correlation with the value of DMB, even if we could not identify muco-cutaneous disorders exclusively present on some aisles of values of the CD4+ lymphocytes in the peripheral blood.

For both sexes, the presence of nutrition disorders is associated with higher values of the DMB versus those registered for the group of HIV infected patients with dermatologic problems but with a normal nutritional status.

The difference is more important for the group of patients with no ARVT (more pronounced for the male patients).

Non-dermatologic co-morbidities are associated with higher values of the dermatologic morbid burden.

The highest values of the DMB were identified in patients with advanced immune suppression, nutritional disorders and other HIV-associated diseases (more obvious for the group of deceased patients at the end of the study).

**The Temporary Association of Dermatologic Diseases**

I have identified temporary associations of dermatologic conditions in patients in all the sub-studies, even in an important amount during 2000-2007 (the multi-annual value: 40.4±3.1%).
Generally, such associations exist and grow in frequency, in cases with a long evolution of the HIV infection. Such cases practically integrate acute/recurrent dermatologic conditions in a chronic muco-cutaneous spectrum of disorders.

One have also noticed a tendency towards the reduction in time of the frequency of such associations (≥3 dermatologic conditions) simultaneously with the generalization and growing of the power of the combined ARV regimens (which also generated a reduction in the average value of DMB/year).

The study showed a direct relationship (not necessarily a causative one) between the multiple associations in time and the poor nutritional status of the HIV infected patients (in itself responsible for some chronic dermatologic conditions).

In the HIV infected patients with associations of muco-cutaneous diseases, we have also noticed in time, the existence of an inverse relationship between the level of the immune suppression and the size of the association.

In a restricted group, which does not allow for the generalization of the results, we have noticed that in the HIV infected patients with multiple associations (≥3 dermatologic conditions), there is a tendency towards the deterioration of the immune status in the next 5-6 months from the diagnosis of the associated dermatologic status.

**Evolutive Dermatologic Patterns in Multiexperienced HIV Teenagers Correlated with the Type of Response to ARVT**

One group of 134 HIV infected patients was clinically, dermatological and immunological followed up - (also virological survey starting with 2002) - from the diagnosis of the HIV infection during the “early” childhood. After a dynamic combination of the above mentioned parameters, I organized the HIV infected patients with dermatologic disorders in relationship with the result of the ARVT (after 2000): “patients with therapeutic success” and “patients with therapeutic failure”; each group was later divided in patients with “concordant” results (i.e. viral load and CD4 level went corresponding favorable results) and patients with “dissociated” results (i.e. only the evolution of one of these two parameters was in an expected direction).

On this matrix, I have then fixed the dermatologic events. Some dermatologic profiles could be outlined, covering 73, 3% from the group (i.e.98 HIV infected patients); the rest of the cases did not undergo classification because of the high deviation of the parameters from these profiles.

The most frequent profile was of the “patients with viro-immunologically success to the cARVT in accordance with the expectations and a diverse spectrum of singular non-related dermatologic diseases” (24 cases, 24,5%).
General Conclusions

I. The dermo-epidemiological study focused on a characteristic sample for the HIV+ population in Romania, meeting the common characteristics of this group (which are also the particularities of this population in the HIV/AIDS pandemics): the horizontal transmission of the infection, which for the majority of cases occurred during hospitalizations, with HIV-1 subtype F, of neonates and small children, born from HIV (-) mothers, during 1987-1990.

Due to its dimensions, the inclusion of patients from various regional centers of survey of the HIV infection from around the country (Craiova, Timișoara, Bucharest), the period of the dermatologic monitoring (14, 9 ± 2,4 years), the study can offer a real dynamic image of the problem addressed, in this special population.

II. The structural design of the study overlapped the historical steps of the ARV treatment in Romania (i.e. the pre - ARVs therapeutic stage: 1990-1995, the transitional stage: 1996-1999, the stage of the ARVs combined regimens - (HAART strategy): 2000-2007.

Thus, via the comparison of the results, we could extract one series of conclusions regarding the effects of the ARVT on the epidemiology of the HIV/AIDS-associated dermatologic conditions.

III. Within the group, during 1990-2007, 78% of the monitored HIV infected persons developed at least one dermatologic disease, which was also reflected in the important proportion (23%) that the dermatologic diseases had in terms of volume of the medical assistance given to this population.

IV. The resulted data from the studies confirmed the importance of the dermatologic diseases among the horizontally HIV infected children. The general profile of this group has common elements with the specific pathology of the vertically infected child, but also elements of the diseases encountered in the horizontally infected adolescent and adult.

V. The number of dermatologic entities extended in time, from 53 in the pre-therapeutic stage to 58 in the HAART era, in direct relationship with the aging of this population, the “ageing” of the HIV infection itself, the multiplication of the ARV therapeutic lines due to the failures and the rise of the muco-cutaneous conditions associated with the ARV medication.

VI. The effects of the combined ARVT had a positive impact in the extension of the life expectancy, the slowing of the progression towards AIDS and the death of the patients. But all these elements favored the expression of specific age-related conditions, of chronic immune inflammation from the HIV/AIDS infection and of adverse reactions and long term toxicity of the ARV products. At the same time, we registered a reduction of the average value of the dermatologic morbidity burden/patient: if in the pre-therapeutic stage, the annual trend of the dermatologic morbidity burden/patient was rising, in the HAART period we have noticed a statistically significant multi-annual reduction. In time, parallel with the ARV therapy generalization, the proportion of patients with muco-cutaneous conditions diminished (from 85%...
in the pre-therapeutic era to 72% in the HAART era).

VII. Every stage of the study was ruled by a limited number of dermatologic disease (i.e. 10 - 12), which totaled 60-80% of the muco-cutaneous pathology registered in these patients. The maintenance in the first positions of the mucous infections, even in the associative therapeutic stage, sustains the important alteration during the HIV infection of the subset Th17 (with implications in the immunity of the mucosa), without an effective repair even during the post-HAART immune reconstruction.

VIII. With the generalization of HAART (and the aging of the patients) we have registered a significant reduction in the weight of the infectious dermatologic conditions in favor of the non-infectious muco-cutaneous diseases (especially the inflammatory ones, allowing for a speculative referral to the “inflammaging” phenomenon described during the HIV infection).

The amplification of the proportion of the miscellanea category is due to the development of the dermatologic conditions associated with the ARV medication.

IX. The gender of the patients made no remarkable difference in the weight of different categories and dermatologic entities or the average value of the dermatologic morbidity burden. But the DMB was significantly influenced by the level of the immune suppression, the presence of non-dermatologic HIV-associated co-morbidities and the nutritional disorders.

X. The association in time of more than two muco-cutaneous conditions in an HIV-infected person under ARVT, must alert the doctor in relation with a possible immune deterioration of the patient in the next 6-9 months.

XI. The dynamic combination of clinical, dermatological, immunological and virological parameters and the dermatologic history, allows for the recognition of a few types of dermatologic profiles.

The most frequent one is that of a patient with “ARV therapeutic concordant viro-immunologically success and a diverse, isolate dermatological pattern”. The validation of such profiles needs supplementary prospective, extensive studies under the surveillance of a dermatologist.

XII. As a result of the data in this study, I consider that the dermatologic examination must be included in the structure of the periodical evaluations within the comprehensive long-term approach of the HIV/AIDS case.

A minimal dermatological training (regarding at least the first 10-12 muco-cutaneous conditions most frequently found among this population) must explicitly be included in the curricula of the HIV/AIDS case managers.

The dermatologist must be included in the multidisciplinary team assuring the monitoring of the infection, providing at least one check-up/semester and must be supplementary trained in the area of the retroviral immunopathogeny and the specific antiretroviral HIV/AIDS treatment.

IX
**Key Words**


Craiova, 01/06/2010