

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA  
DOCTORAL SCHOOL**

**PhD THESIS**

**HIV/AIDS INFECTION IN CHILDREN WITH TUBERCULOSIS IN DOLJ COUNTY  
AND NEIGHBORING COUNTIES**

**ABSTRACT**

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## INTRODUCTION

Over time, the world was devastated by numerous epidemics. These including HIV infection and tuberculosis infection with *Mycobacterium tuberculosis* put the serious problems in the implementation of prevention globally strategies. Despite all the efforts of the World Health Organization, governments and other non-governmental organizations, co-infection HIV-TB remains one of the major problems of public health, through both increased mortality and the enormous costs for prevention, diagnosis and treatment .

There is a complex relationship between the two diseases, that fact, feeds synergistically both epidemics, increase both morbidity and mortality attributed to each part infections. One in eight cases of tuberculosis occur in people with HIV, a quarter of all deaths from tuberculosis in people living with HIV is registered and a fifth of deaths due to HIV infection in people with tuberculosis are recorded.

## HIV / AIDS EPIDEMIOLOGY

According to published data by UNAIDS and WHO, from the beginning of the HIV/AIDS infection and to the present, over 25 million people died from it. In 2013, globally, there were approximately 35 million people living with HIV, of which about 16 million women and 3.2 million children under of 15 years. The biggest epidemics in sub-Saharan Africa have stabilized or signs of decline, while in many countries in Eastern Europe (Russian Federation, Ukraine) and Central Asia, HIV incidence show an increase of over 25% . Injecting drug use is the major route of HIV transmission in this region, and the central role in transmission of infection, returns sexual partners of drug users so. As regards cases of emerging infections in children in 2013 were found approximately 240,000 children lower than 58% in 2002, considered the year with the highest number cases of infection. This demonstrates the effectiveness of strategies for prevention and control of this infection in this population, but to eliminate it in children, is a long way.

The number of AIDS deaths in 2013 is 1.5 million people and the number of people who receiving antiretroviral therapy amounts to about 13 million people, only one in four children receiving antiretroviral therapy and 38% of adults are infected with HIV have access to antiretroviral treatment.

Since the beginning of infection in Romania, 1985 and 2014, reported a total of 19,261 infected persons with the human immunodeficiency virus that 9946 children aged between 0 and 14 years. In 2013, the number of people living with this infection in Romania is 12,273, of which most cases, 7,012 met the group 20-29 years and 202 cases in children less than 14 years.

## HIV / AIDS EPIDEMIOLOGICAL PROCESS

***The source of infection*** is the people infected with HIV, regardless of status or clinical expression of infection, persistent infection is acceptable for life.

### ***The transmission***

*Sexual transmission* is via the genital mucosa, anal or oral. Rectal mucosa epithelium single ply because it is the most susceptible to infection. This type of transmission remains predominant in 70-85% of cases being involved. Women are more prone to this infection than men, 0.1-0.2% for a single sexual contact with an HIV infected man to 0.05-0.1 for a heterosexual contact with an HIV infected woman. Transfers may be either heterosexual or homosexual contact, the receptive partner is the most exposed to infection (man having sex with man).

*Parenteral transmission* is through direct contact between infected blood and body receiver. This type of transmission include several categories of persons are most commonly affected. Among them hemophiliacs, politransfuzatii, recipients of organs, which transmission is achieved by blood, blood products or tissues; people who inject drugs through needle and syringe reuse and healthcare professionals through needle prick, open wounds or mucous membranes with blood exposed.

Mother to child HIV transmission can be: antepartum (in the last weeks of pregnancy with severe child development and prognosis), intrapartum (most frequent during labor and expulsion, when the child enters conjunctival mucosa in contact with blood or genital secretions of infected mothers, either by ingestion thereof), postpartum (through breastfeeding).

***Responsiveness*** is universal and general infection but some populations have a higher risk of infection by certain practices of life and human behavior. However women are at a higher risk of infection than men.

### **ANTIRETROVIRAL THERAPY**

Antiretroviral therapy aims four major objectives: to alleviate clinical endpoints and even separate the clinical signs of disease; virological objectives which seek to reduce the amount of viral as possible; immunological targets require increased CD4 count as close to normal and epidemiological targets aimed at reducing HIV transmission to others.

All guides recommend starting treatment in the following cases: presence of clinical symptoms of secondary diseases which show the presence of immunodeficiency, decreased CD4 +, presence of active HIV replication as measured by HIV RNA level. Treatment of infants infected with HIV is a challenge because of the rapid progression of the disease, high viral load and the few existing drug options for this age.

### **HIV / AIDS**

World Health Organization requires four major objectives: reducing new infections among young people by 50%, eliminating new HIV cases in children by 90%, reducing the number of deaths due to HIV infection by 25% and reducing deaths from tuberculosis by 50%. Since 2010, UNAIDS, including antiretroviral therapy as an essential pillar in the overall strategy to control the spread of HIV and its administration proposed: to all people living with HIV who have CD4 cell counts below 500 / mm<sup>3</sup>, serodiscordant couples in people with HIV-TB co-infection, pregnant women and children under 5 years of age, regardless of the number of CD4 + cells. In addition to antiretroviral therapy are recommended: testing for HIV and other sexually transmitted diseases, condom use both the masculine and the feminine type (provides protection by

over 85%), male circumcision (reduce risk of transmission from woman to man through sexual contact, by about 60%), free programs for needles, syringes, condoms to people who use drugs by injection.

#### TUBERCULOSIS EPIDEMIOLOGY

Tuberculosis remains one of the major public health problems globally through evolution to chronic and widespread in the population. The infection may extend the lifetime without the disease trigger. A third of the population is affected by infection, latent Mycobacterium tuberculosis. About 10% of these people will be diseases of tuberculosis, half of them in the first 2 years after infection. Following tuberculosis children and adults die more than from any other infectious diseases. In the world every 10 seconds a person dies of tuberculosis. Every 4 seconds a persons sick with tuberculosis. Each untreated can become infected with TB annually between 10 and 15 people. 80% of tubercular patients aged between 15 and 45 years.

In 2013 about 9 million people were affected by tuberculosis, more than half (56%) were recorded in Southeast Asia and the Western Pacific. In the European region there were 353,000 new cases of tuberculosis and 35,000 deaths from the disease in 2012. In 2013, in Romania, the overall incidence of tuberculosis was 78.58 to 100,000 inhabitants, the number of patients with tuberculosis was 16,711 cases and mortality was 5.3 per 100,000 population.

#### TUBERCULOSIS EPIDEMIOLOGICAL PROCESS

**Source of infection** is represented by patients with pulmonary tuberculosis, particularly hollow shapes, intense bacilifere and still untreated, chronic patients, patients refractory to treatment, patients paucibacilari and patients with fistulising forms of pulmonary tuberculosis. Animal source of infection in this disease is represented mainly by cattle that can transmit the infection to humans through milk, urine or faeces.

##### **The transmission:**

Air-borne particle inhalation Way bacilifere able to get closer to the peripheral airways. A person suffering from tuberculosis eliminates the surrounding space through coughing, sneezing, sang and talked drops bacilifere, after removing the water from them and drying them, turns to dust bacilifer. It can retain virulence in the environment for several weeks and can lead to infection of many people around the patient.

The path for the transmission of Mycobacterium bovis specific digestive.

Dermal described in persons handling pathological products that come from tuberculosis patients: pathologists, laboratory, necropsy.

##### **Responsiveness population**

10-20% of subjects infected with tuberculosis will îmbolnăvii. In these anti-infective defense mechanisms are compromised due to numerous factors related to age related diseases, social and economic factors, etc;

## **DIAGNOSIS OF CHILD TUBERCULOSIS**

### **Tuberculosis diagnostic criteria in children**

**The probability** (any three of the following): contact with a source confirmed or suspected TB; Persistent symptoms and signs of TB as cough, fever, weight loss, fatigue, changes respiratory rates on lung examination, lymphadenopathy; positive tuberculin test (> 10 mm); radiological changes as lymphadenopathy or infiltrates; histopathology suggestive of TB.

**The certainty:** positive cultures Mt gastric aspirate or other products.

## **CHILD TUBERCULOSIS THERAPY**

Treatment for both, adult and child has the following purposes: healing the case, reducing the risk of recurrence, prevent deaths, prevent the onset of chemoresistance Mt, preventing complications.

Regimen consists of two phases: the initial two month long is administered daily 4 antituberculosis drugs: isoniazid, rifampicin, pyrazinamide and ethambutol and continuation phase, which lasts four months and isoniazid and rifampicin is administered in three doses week.

## **TUBERCULOSIS PREVENTION IN CHILDREN**

The main objectives of prevention work are limiting the spread of infection and disease, and decrease as much as possible the number of deaths. This is achieved by tuberculosis at an early stage in drug prevention and specific.

Drug prophylaxis on the one hand protects uninfected persons who are exposed to contagious infection sources (primary prevention), on the other hand reduces the risk of progression of infection to disease (secondary prevention). It addresses in particular children under 5 years.

### ***BCG vaccination***

BCG vaccination is a method of active immunization but did not prevent infection by Mycobacterium tuberculosis and do not interrupt the chain of the disease epidemiology. It is highly useful for preventing serious cases of illness which may occur in young children (tuberculosis meningitis and miliary tuberculosis), and is mandatory in areas with high tuberculosis endemia.

### ***New tests available for the diagnosis of latent tuberculosis infection***

Since tuberculin testing (TST) is practiced in 1930, recently were discovered other tests for diagnosing latent tuberculosis infection called interferon gamma release assays (Interferon Gamma Release Assays - mold), which are more sensitive and more specific than TST tuberculin but more expensive and tested mainly on adults. Approved two tests TB<sup>®</sup> QuantiFERON-Gold-in-Tube test (QFT-GIT) and T-SPOT<sup>®</sup> TB test.

Particular aspects of co-infection HIV / TB According to data from the World Health Organization estimates that about 1.1 million people (13%) of the 9 million people with tuberculosis were detected in 2013 were HIV positive . One third of HIV-infected persons are infected with latent tuberculosis. Tuberculosis is the most common cause of death in people affected by AIDS, representing approximately 25% of deaths and the most common opportunistic infection associated with HIV and an important factor in

the acceleration of HIV to AIDS. In turn, HIV is a key factor behind the high incidence of recurrence of TB globally. It is a risk factor for developing tuberculosis reactivation of latent infection and accelerate disease progression to tuberculosis infection. HIV positive risk 20-30 times more likely to develop tuberculosis compared to uninfected persons. Prevalence in children with HIV infection tuberculosis, varies from 10 to 60%. Treatment of tuberculosis in HIV-infected child should be started as early as possible, even after diagnosis of tuberculosis, representing a priority in the management co-infection HIV-TB treatment in children. Antiretroviral therapy should also be initiated as soon as possible taking into account the clinical and immunological criteria of the child. Prevention and control activities for both infections take place in collaboration following three major steps: increased measures to detect all cases of HIV and TB, isoniazid preventive therapy and TB infection control.

#### **OBJECTIVES OF THE STUDY**

Based on all the issues raised in general, this paper aims to expose personal experinşa in assessing co-infection rate of HIV / TB in the pediatric population in Dolj County and neighboring counties.

Thus we had the following objectives:

- Analysis of the frequency variations of HIV infection in children
- Analysis and tuberculosis in children
- Analysis of co-infection HIV / TB in the pediatric population
- Identify and epidemiological profile of co-infection risks associated with HIV / TB

#### **MATERIALS AND METHODS**

IT's a retrospective, observational, study. The total number of cases of HIV / AIDS in the records of the Regional Centre for Surveillance and Monitoring of HIV / AIDS cases Craiova was 827 but by establishing criteria for inclusion in the study, which are consistent with the case definition of HIV / AIDS child (CDC Atlanta 1993) have defined a sample of 539 cases aged between 0-15 years after diagnosis, conducted in 1990-2012. The data used were obtained retrospectively from monitoring forms patients , the Regional Centre for Surveillance and Monitoring of HIV / AIDS in Craiova Hospital for Infectious Diseases and Victor Babes Pneumoftizilogie,,,, Craiova.

Were formed subgroup variables of interest followed:

- Gender (male / female)
- Environment origin (urban / rural)
- County of origin
- Age groups

For co-infection HIV-TB expression in children, have been used: absolute frequency, incidence, cumulative incidence.

Data processing was performed using statistical computing applications by establishing correlation tests between two numeric variables and chi-square test and Fisher exact tests using simple and multiple linear regression.

## **RESULTS AND DISCUSSION**

### ***1.1. Distribuția lot with regard to sex***

Of the 539 cases, there is a slight predominance of cases in male children (289 cases, representing 53.53%) than female children (250 cases, representing 46,47%). Sex ratio (M / F) is 1.15.

### ***1.2. Batch distribution by area of origin***

Of the 250 cases of HIV infection in females, 68 cases, accounting for 27.20% had at least one episode of tuberculosis infection during the study, compared with 77 cases, representing 26.74% detected among male children.

### ***1.3 lot gender distribution according to the association of tuberculosis infection***

Of the 250 cases of HIV infection in females, 68 cases, accounting for 27.20% had at least one episode of tuberculosis infection during the study, compared with 77 cases, representing 26.74% detected among male children.

### ***1.4. Distribution lot with regard to the residence and association tuberculosis infection***

There is a predominance of cases of co-infection HIV-TB in rural areas 85 which cases, representing 31.02% compared with 60 cases in urban areas, representing 22.73%.

### ***1.5. Repartiția sex depending on when TB infection***

Female gender was represented by 43 cases, accounting for 63.24%, while the male is represented by only 49 cases, representing 63.64%, a percentage similar to that of female cases.

## **Comparative II. Analiza association with HIV-TB cases and only those with HIV**

### ***II.1. Distribution of cases by sex***

The incidence of HIV-TB co-infection is similar in male cases (17.01%) and in the female (17.13%) in the group of co-infection HIV-TB with ratio sex ratio was 1.13.

### ***II.2. The distribution of cases by area of origin***

Of the 92 cases of HIV-infected children who were associated tuberculosis infection by the age of 15 years, a total of 54 cases were in rural area of origin, incidences were 58.7%. In contrast the number of cases from urban areas was almost 7% lower incidences of urban area of origin thus 41.3%.

Identifying a higher frequency of cases from rural areas, has imposed its pursuit depending on the time of birth. Starting from the specific knowledge Romania phenomenon discussed two different contexts: one before the year 1990, which was cvasipredominant parenteral transmission of infection and after 1990 characterized by the predominance of vertical transmission, we found that the cohort born before 1990, over 60% of cases (61.6%) were from rural areas. In children with HIV-TB confection, born after 1990, marked the origin ruralization cases decreased. Distribution of cases in the two backgrounds balancing the share of children in rural areas decreased to 47.4% is lower than the frequency of cases from urban areas.

Was a 1.33 times higher risk of TB co-infection in children from rural areas compared with those who came from urban areas (RR - 1.33, CI95% 1.05 - 1-69; p = 0.02 )

Analysis of the distribution of cases belonging to the region Oltenia counties: Dolj, Olt, Gorj County, capture a greater share of cases came from Dolj County. Dolj and Olt has accumulated 55% of co-infection HIV-TB cases (50 cases out of 92) were derived from Olt County 17 cases representing 40% of all TB HIV lot. The two counties together

accounted for most of the cases identified in the four counties of the region included in the study. Thus 95% of cases of HIV-associated tuberculosis and just as many of those with HIV infection came from those counties. It is remarkable that for 3 of the 4 cases with rural counties share was higher compared to urban areas in the group of co-infection HIV-TB .

### **II.3. Age considerations cases**

Age cases was about 9 years old. Although there was a slight difference in the mean age between the two groups, being higher in cases with tuberculosis (IC95% 8.84 years from 8.040 to 9.634) than that recorded in the group of cases of HIV infection only (8.22 years; IC95% from 7.849 to 8.594) that was not statistically significant. ( $p = 0.18$ ). In males, age was not significantly different from the comparative analysis of the average values in the group of cases co-infection HIV-TB (8.98 years) and only those with HIV (8.42 years). For girls, the difference was so small in the two groups, accounting for nearly nine years female cases in the batch co-infection HIV-TB with 8.42 years and the female cases the only group with HIV, is also no statistical significance ( $p = 0.034$ ).

In Mehedinți county, the average age of detection of cases in the group with co-infection HIV-TB is double the average age of detection of cases in the group without tuberculosis infection. The slight difference is observed in Olt County.

The numerous cases of co-infection HIV-TB belonged to the age group between 10 and 15 years in this age group were identified 43 cases accounting for nearly half of all co-infection HIV-TB cases.

### **II.4. Distribuția cases the route of transmission**

As regards the mode of transmission of HIV infection in the two groups, easily observed that the most common route of transmission of HIV infection was parenteral route. 87 cases (94.6%) out of 92 cases of co-infection group of children with TB were infected in this way and 427 cases (95.5%) in the group of children without co-infection presents the same way transmission.

Distribution of cases according to the method of HIV transmission in urban areas have the same features. The most common route of transmission of HIV in the two groups of children, co-infection HIV-TB one with and only with parenteral transmission of HIV infection, there is even a percentage equal in the two groups, 94.7% of all cases . The same distribution of cases is maintained in rural areas where 264 children from both groups presented broadcast-parenteral route (51 children in the group of co-infection with 213 children in the group without co-infection, out of 275 children .

### **II.5. Analysis cases according to clinical stage**

Most cases, 403 were diagnosed disease state B, 127 cases were diagnosed in stage C disease and only 9 in the state of a disease.

### **II.6. Distribuția cases by the presence of other infections associated**

#### ***II.6.1. Serological evaluation of antibodies to Toxoplasmosis***

Most cases received serological evaluation of anti-Toxoplasmosis antibodies, a number of 88 cases out of 92 in the group of HIV-TB co-infected (95.65%) cases were tested and in group without co-infection rate was testing low, a total of 363 cases out of 447 were tested.

The risk of antibodies to Toxoplasmosis was almost 50% higher in HIV-TB group compared with HIV group, the relative risk value of about 1.5. (RR 1.46; CI95% 1.03 to 2.13;  $p = 0.048$ ).

The cases in rural areas showed positivity for anti Toxoplasmosis almost half of the cases (44.4%) in group HIV-TB unlike HIV lot where the incidence of antibodies to Toxoplasmosis serologic evaluation was to 29%. Urban presented a different situation from that observed in cases in rural areas. For children from urban areas, the incidence of antibodies to Toxoplasmosis was similar in both groups.

Incidence Toxoplasmosis antibodies was higher in group cases with HIV and TB co-infection (group HIV-TB) in all counties.

### ***II.6.2.Evaluarea of antibodies to VMC serological***

Incidence of antibodies to cytomegalovirus was higher in group HIV to HIV-TB group (23.9%. Compared with 18.5%.) But not surprised statistical significance of this difference. Rural areas showed an incidence of antibodies to cytomegalovirus in the group of cases with HIV-TB co-infection (11.11) by more than 50% lower than the HIV group (18.55%), with statistical significance ( $p = 0, 0015$ ). On the basis of differences seroprevalance in rural areas and rural areas in the group who had co-infection cases, we could calculate the risk of anti-cytomegalovirus antibody present more than 2 times higher in rural children with HIV-TB co-infection compared to children in rural areas (RR = 2.22; 95% CI 1.0733 to 5.5024;  $p = 0.046$ ). One in five children with HIV is co-infected with cytomegalovirus unlike those with co-infection HIV-TB and VMC that co-infection is present just one of 10 female children.

### **II.6.3.Evaluarea serological presence of antibodies against hepatitis B and C viruses**

A total of 27 cases in the group with positive serology for coinfection had hepatitis B virus infection HBV prevalence was 29.35%. not identified differences compared to batch HIV positive serology for HBV that was identified at the same rate (29.08%).

Children in both groups were not identified but two cases of HCV infection, which are distributed equally in each case one of the two groups.

### **II.7.Analysis mortality HIV-TB co-infected cases compared with HIV**

In the HIV-TB co-infected batch at the end of the study had died a number of 38 cases out of 92 cases that were the study group. Mortality in this group was 41.3% .In only among HIV infected cases, the number of cases rose to 128 dead, allowing generated a lot of mortality from HIV (28.6%) with about 50% lower compared to group HIV-TB.

In particular, drew attention to the situation in rural areas where deaths, mortality in HIV-TB group was 48.1% compared with mortality in cases where the lot without co-infection was 33%. In urban areas, mortality in HIV-TB group was 31.6% and the HIV group expressed a mortality of 24.3%.

The risk of death in males, which come from the group of children with co-infection HIV-TB is more than 1.5 times the risk of death in males belonging to the group of children with HIV only. This is demonstrated with statistical significance (RR = 1.5, IC95% = 1.0788 to 2.1891,  $p = 0.01$ )

Most deaths occurred in the age group 5-9 years, 42.4% of children 5-9 years of co-infection HIV-TB group with 34.4% of children and 5-9 years in the group of only with

HIV infection. But most deaths are recorded in the age group 10-14 years among children with co-infection HIV-TB, 44.2%.

Analysis of mortality in cases with parenteral transmission showed a mortality rate of 40.2% in HIV-TB group and 28.3% in group HIV. Although there were only 19 cases of vertical transmission has been implicated in both groups of children studied, almost half of them died (9 cases out of 19). Mortality in the group of children with HIV co-infection TB was 60% higher than the mortality of children with HIV infection only, where it was 42.9%,

Analysis of mortality according to the clinical stage of HIV / AIDS, shows, as has been shown, that mortality is proportional to the clinical stage of infection, 26% in stage A stage disease and 45.8 C disease.

Toxoplasmosis infection association, has no negative effect on mortality associated with both groups of children in studio.

Instead association CMV infection with co-infection HIV-TB has led to increased mortality in these cases, 47.1%.

And hepatitis B infection associated with co-infection HIV-TB influenced the prognosis of this co-infections, mortality in co-infection HIV-TB consignment and positive serology for hepatitis B was 51.9% compared to 38.1% children with negative serology for the virus.

#### CONCLUSIONS

1. Incidence of tuberculosis infection among HIV infected cases was 17.07%. The frequency of tuberculosis is generally known to be higher in rural areas, poverty, living standards and education leading to maintain a higher frequency of tuberculosis in rural communities. This affects the frequency of tuberculosis in children in these areas, rural a suggesting that there was a significant exposure to tuberculosis in HIV infected children, establishing a 1.33 times higher risk of tuberculosis in children garment from rural areas compared with those who came from urban areas.
2. It was observed a mean age at detection of cases, more cases of HIV coinfection group those with TB, comparativ with just those with HIV in all counties. Age group 10-15 years was almost 10% better represented in HIV-TB group compared to infected only with HIV, it the high frequency of tuberculosis adolescents, and Uneo paerioade higher risk tuberculosis infection in children higher ages.
3. As regards the mode of transmission of HIV infection in the two groups, the most common was the parenteral route. This is explained by the fact that some of these children are part of the cohort 1990s, when the transmission was predominant in this way.
4. The inclusion of tuberculosis as a criterion in stadialisations developed by CDC AIDS has led to a rate of almost 4 times higher stage C disease in HIV co-infected TB cases even at initial staging compared with only HIV cases.
5. The risk of antibodies to Toxoplasmosis was almost 50% higher in HIV-TB lot compared with HIV, the value of the relative risk of about 1.5, the observed frequency and a higher risk cases in rural areas (45%) exposure to sources being

- the most common in this environment compared to urban areas, where the incidence of antibodies to Toxoplasmosis but was similar in both groups.
6. Incidence of antibodies to cytomegalovirus was higher in group HIV to HIV-TB group, the presence of antibodies against cytomegalovirus identify risk was almost 40% lower in HIV-TB co-infected cases compared with only HIV risk being lower for HIV co-infected TB cases, especially in rural areas. He could see a noticeable different toxoplasmosis being more frequent in rural areas and rare cytomegalovirus infection.
  7. The impact of tuberculosis on survival was important, being identified excess mortality in HIV-TB co-infected cases, the risk of death in HIV-TB group was 1.5 times higher compared with HIV lot. A proof of the effect atra out strong association between mortality and background, which substantially increases the risk of death beyond the association of tuberculosis infection in HIV infection. In this regard it has been observed that both HIV-TB co-infected group of those without co-infection and the risk of death was higher for rural children compared to those in urban areas.
  8. Mortality analysis by gender, it was noted that mortality among people male co-infection HIV-TB was 46.9%, almost half of the males in this sample, dying during the study, the risk being higher in boys than girls.
  9. Mother to child transmission was associated with high mortality compared the parenteral transmission.
  10. The association of infection with Toxoplasmosis, had a negative effect on mortality associated with both groups of children in the study, however, the combination of TB and HIV-infection with cytomegalovirus, and hepatitis B to double the mortality.

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