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# Human Immunodeficiency Virus - Related Laboratory and Clinical Manifestations

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**Abstract**

*Human immunodeficiency virus* **(***HIV*) is a member of the family *Retroviridae* that attacks the immune system of the infected person. The virus destroys a type of white blood cell (T helper cells or CD4+ cells) and gradually breaks down a person's immune system. As many as 37 million people worldwide are thought to be infected. In our retrospective study, we review the clinical evidences as a reason for association with *HIV* infection and the most common co-infections in patients living with *HIV*. Since 2003 we have tested 148 *HIV* infected patients (104 males and 44 females), aged between 3 months and 67 years, average age 37.3 years. Out of the patients investigated, 108 were with proven HIV-positive status (persons living with HIV), hospitalized in "St Marina" University Hospital, Clinic of Infectious, Parasitic and Dermatovenerologic Diseases and 40 patients were found with reactive results at our Virology Laboratory and confirmed as *HIV* infected at the National *HIV* Reference Laboratory in Sofia. ELISA *HIV* Ag&Ab (DiaPro Italy), *HbsAg* (SURASE Taiwan), *Anti Hbc* (DiaPro Italy), *Anti HCV* (NANBASE Taiwan), Anti *CMV* IgM/IgG (EUROIMMUN Germany), Syphilis Ab screening (EUROIMMIN - Germany) were performed according to the manufacturer's recommendations. Out of the 40 investigated patients with diagnostic and therapeutic problems, 13 (32.5%) were with clinical diagnosis pneumonia, 6 (15%) with lymphadenoipathy, 5 (12.5%) with hepatitis, 3 (7.5%) with mononucleosis-like syndrome, 4 (10%) with wasting syndrome and chronic diarrhea, 4 (10%) with neurological sympthoms, 3 (7.5%) with dermatological manifestation including Herpes zoster, and 2 (5%) were mothers of infected children. Out of the 108 pre-defined *HIV* infected patients, we received serological data for hepatitis B in 12 (11%), hepatitis B/C co-infection in 2 (1.9%), hepatitis C in 6 (5.6%), syphilis in 24 (22.2%), CMV active infection in 21 (19.4%). The most common reason for HIV testing is the diagnosis bilateral pneumonia, unsusceptible to conventional antibacterial treatment. People living with *HIV* most often were co-infected with syphili*s*.

**Keywords**: *HIV,* pneumonia, hepatitis B (*HBV*), hepatitis C (*HCV*), syphilis, co-infections.

**Резюме**

Човешки имунодефицитен вирус **(***HIV*) принадлежи към семейство *Retroviridae*. Атакува предимно белите кръвни клетки (CD4 + клетки) и срива имунната система на заразения индивид. Около 37 млн индивиди по света са инфектирани. Целта на настоящото изследване е да се анализират най-честите клинични симптоми, водещи до доказване на HIV серопозитивност и най-честите ко-инфекции при пациенти, живеещи с HIV. В периода 2003-2017 са тествани 148 *HIV* инфектирани пациенти (104 мъже и 44 жени) на възраст 3 м. - 67 г., средна възраст 37.3 г. От изследваните пациенти 108 са с доказан HIV позитивен статус, хоспитализирани в Клинката по Инфекциозни болести, паразитология и дерматовенерология на УМБАЛ ,"Света Марина" - Варна и 40 са доказани като позитивни в Лабораторията по Вирусология и потвърдени в Националната референтна *HIV* лаборатория - София. Приложени са търговски ELISA тестове, *HIV* Ag&Ab (DiaPro Italy), *HbsAg* (SURASE

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Taiwan), *Anti Hbc* (DiaPro Italy), Anti *HCV* (NANBASE Taiwan), Anti *CMV* IgM/IgG (EUROIMMUN Germany), *Syphilis* Ab screening (EUROIMMIN - Germany) съобразно изискванията на тест процедурата. От изследваните 40 пациенти с диагностични и терапевтични проблеми 13 (32.5%) са с клинична диагноза пневмония, 6 (15%) с лимфаденопатия, 5 (12.5%) с хепатит, 3 (7.5%) с мононуклеоза подобен синдром, 4 (10%) с хронична диария и загуба на тегло, 4 (10%) с неврологична симптоматика, 3 (7.5%0 с дерматологична симптоматика включително Herpes zoster, артралгия с обрив и 2 (5%) са майки на HIV инфектирани деца. От 108-те HIV инфектирани пациенти са установени серологични данни за хепатит В при 12 (11%), хепатит В/С ко-инфекция при 2 (1.9%), хепатит С - 6 (5.6%), сифилис 24 (22.2%), активна *CMV* инфекция при 21 (19.4%). Данните показват, че най-честа клинична манифестация като основание за *HIV* тестване и доказване на серопозитивност е двустранна пневмония, неподдаваща се на лечение с конвенционални антибактериални средства. Лицата живеещи с *HIV* инфекция най-често са ко-инфектирани със сифилис.

**Introduction**

*HIV* is a member of the family *Retroviridae* that attacks the immune system of the infected person. The virus predominantly destroys a type of white blood cell (T helper cells or CD4+ cells), and gradually breaks down a person's immune system. As many as 37 million people worldwide are thought to be infected (Platt *et al*., 2016). There are three stages of *HIV* infection. Stage one lasts 2 - 4 weeks with flu-like symptoms, but not everyone will experience this. Stage two may last for 10 years or so, without any apparent symptoms. Stage three is when the immune system has been so badly damaged that it can no longer fight off serious infections and diseases. The symptoms of *HIV* can differ from person to person and some people would not experience symptoms at all for many years. AIDS-related complex or persistent generalized lymphadenopathy syndrome, fever, weight loss, night sweats, diarrhea, pneumonia are possible (Vanhems *et al.,* 2002). Viral opportunistic infections such as *CMV*, or co-infections with other human viruses can be found as well. People living with *HIV* are at higher risk of developing other infections such as hepatitis B, hepatitis C, which can aggravate disease management (Alter, 2006). As many people do not have any symptoms in stages one and two, *HIV* often spreads through people who simply are not aware they are infected. The diagnosis of HIV infection is usually based primarily on serological tests. ELISA is the most commonly used method for screening of blood samples for *HIV* (Maskill *et al*., 1998).

The aims of this retrospective review study are to investigate the clinical manifestations as a reason for *HIV* testing and the most common co-infections of patients living with *HIV* in the Northeastern Region of Bulgaria.

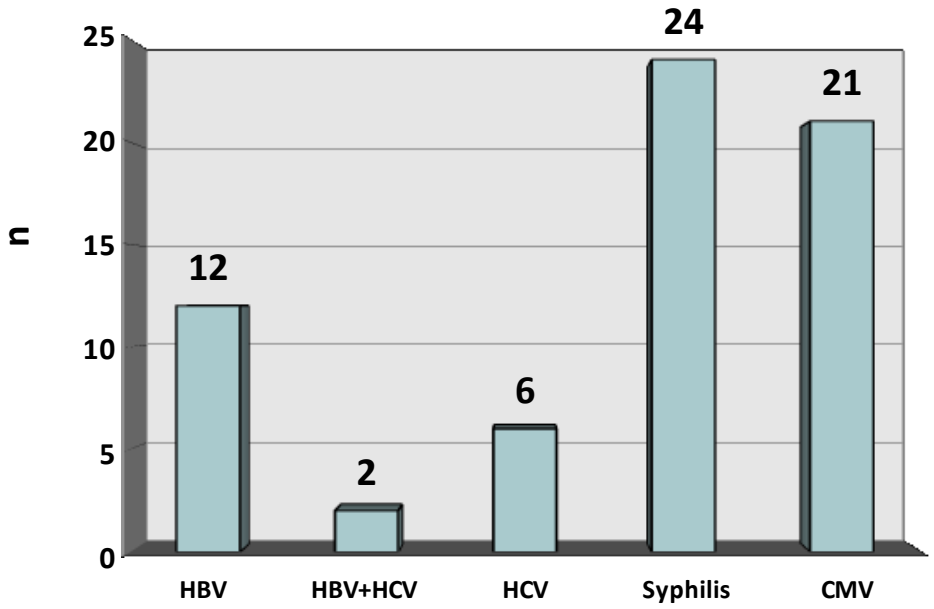


**Fig. 1.** Co-infections in pre-defined patients living with *HIV.*

## Materials and Methods

*Study population*

Between 2003 and 2017, we tested 148 *HIV* infected patients (104 males and 44 females), aged between 3 months and 67 years, average age 37.3 years.

Out of the patients investigated, 108 were people living with HIV, hospitalized in the "St. Marina" University Hospital, Clinic of Infectious, Parasitic and Dermatovenerologic Diseases and 40 patients were found with reactive results at the Virology Laboratory, "St. Marina" University Hospital - Varna, Bulgaria and confirmed as *HIV* infected at the National Reference *HIV* Laboratory.

*Method*

ELISA HIV Ag&Ab (DiaPro Italy), HbsAg (SURASE Taiwan), Anti Hbc (DiaPro Italy), Anti HCV NANBASE Taiwan), Anti CMV IgM/IgG (EUROIMMUN Germany), Syphilis Ab screening (EUROIMMIN - Germany) were performed according to the manufacturer's recommendations.

## Results

Out of the 108 pre-defined patients living with *HIV* infection, we received serological data for hepatitis B in 12 (11%), hepatitis B/C co-infection in 2 (1.9%), hepatitis C in 6 (5.6%), syphilis in 24 (22.2%), *CMV* seroprevalence, determined by anti *CMV* IgG positivity was 97% in 102/105 investigated patients. Active *CMV* infection with anti *CMV* IgM positivity we found in 21 patients (19.4%) (Fig. 1).

Out of the 40 patients with diagnostic and therapeutic problems investigated in our laboratory, 13 (32.5%) were with clinical diagnosis bilateral pneumonia, 6 (15%) with lymphadenopathy, 5 (12.5%) with hepatitis, 3 (7.5%) with mononucleosis-like syndrome, 4 (10%) with wasting syndrome and chronic diarrhea, 4 (10%) with neurological symptomatic, 3 (7.5%) with dermatological manifestation including Herpes zoster, arthritis with rush, and 2 (5%) were mothers of infected children (Fig. 2).

## Discussion

*HIV* infection has a broad spectrum of clinical manifestations, ranging from asymptomatic seroconversion to a severe symptomatic illness, resembling mononucleosis or other medical conditions including hepatitis, meningoencephalitis, or pneumonitis. More severe *HIV* symptoms may not appear for 10 years or more after *HIV* first enters the body in adults, or within two years in children with congenital or intranatal *HIV* infection. Without clinical alertness, the illness is usually misdiagnosed or even not considered (Huang *et al*., 2005). In our retrospective study, the clinical symptoms as a reason for *HIV* testing in 13/40 (32.5%) newly diagnosed *HIV* positive patients was pneumonitis, unsusceptible to conventional antibacterial drug treatment (Fig. 2). In this group, one 3-month-old baby with congenital *HIV* infection was included. Pneumonia in immunocompromised patients is a severe infection and inflammation of the lower respiratory tract, often complicated by widespread multidrug antibiotic resistance. The most typical finding of chest radiography includes infiltrates with consolidation, peribronchovascular lesions, and nodular space-occupying lesions, and some findings are correlated with certain etiologies of pulmonary infection (Boyton, 2005; Feldman, 2005).

Lymphadenopathy is one of the most common manifestations at any stage of *HIV*/AIDS with different underlying pathogenesis. It may be the first indication of a serious local or systemic condition. In an Iranian study (Azaz Hadadi *et al*., 2014), 40.45% of *HIV*-infected patients had lymphoadenopathy. In our study, lymphoadenopathy is the cause of *HIV*-testing in 6 (15%) of the newly diagnosed patients. Such symptoms were present in one of the infected children, 6 years of age. In our study group, 3/40 (7.5%) of the investigated patients were with mononucleosis-like syndrome.

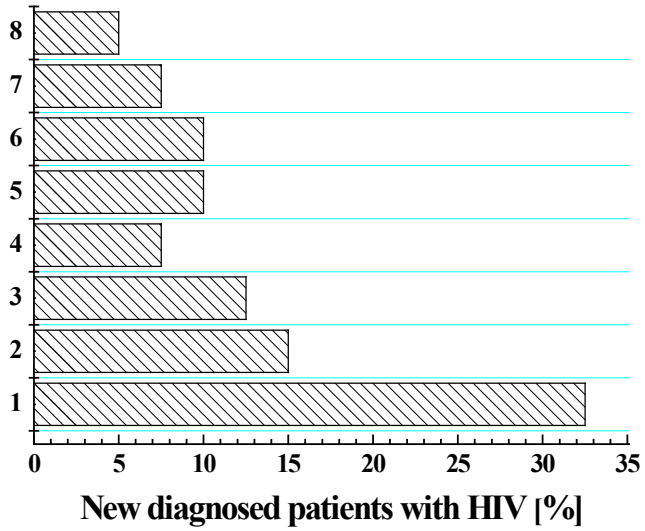


**Fig. 2.** Clinical manifestations in newly diagnosed patients with HIV. 1 - pneumonia; 2 - lymphadenopathy; 3 - hepatitis; 4 - mononucleosa like sindrome; 5 - wasting syndrome+diarrhea; 6 - neurological symptoms; 7 - dermatological manifestation (hzv); 8 - mother of infected child

Infectious mononucleosis-like syndrome may be due to the *Epstein-Barr virus*, *Cytomegalovirus*, *Toxoplasma gondii* and *HIV* infection. Our data correlate with the data of Bottieau (Bottieau *et al*., 2006), where infectious mononucleosis-like syndrome due to *HIV* was detected in 5/72 (6.94%) of the febrile travelers returning from tropical regions. In the context of *HIV* there exists a high rate of new or concomitant infection with certain types of viral hepatitis. In our study, 5/40 (12.5%) of the newly diagnosed *HIV* positive patients were with clinical and laboratory data of hepatitis, - 2 with clinical data of acute hepatitis, 1 - with clinical diagnosis toxic hepatitis, and 2 - with exacerbation of the chronic stage. The other reasons of *HIV* testing and positivity determination in our retrospective study were wasting syndrome and chronic diarrhea. These symptoms were demonstrated in 4/40 (10%) of the newly diagnosed patients. Neurological symptomatics (meningiencephalitis, Bell's palsy, encephalitis) were other clinical manifestations and we found *HIV* seropositivity in 4/40 (10%) of the patients investigated. CNS infection with *HIV* will remain a highly relevant topic for study and investigation. To the study (Levy *et al*., 2010), 21/325 (6.5%) atypical aseptic meningitis were relaterd to *HIV*-infected patients. Dermatological and neurological manifestations, including recurrent herpes zoster and arthralgia with rush, were the symptoms in 3/40 (7.5%) newly diagnosed *HIV* positive patients in our study. One of them was syphilis co-infected. Of the investigated patients, 2/40 (5%) were *HIV* positive mothers of infected children without any clinical symptoms (Fig. 2).

The investigated patients in the present study were not aware of their *HIV*-positive serostatus before our testing that is why the duration of infection, its onset, and route of transmission are unknown.

People living with *HIV* are at higher risk of developing other infections such as hepatitis B, hepatitis C, which can make disease management difficult. *HBV, HCV* and *HIV* share common routes of transmission, but they differ in their prevalence by geographic region and the efficiency by which certain types of exposure transmit them. In *HIV*-infected persons, an estimated 2-4 million have chronic *HBV* co-infections, and 4-5 million have *HCV* co-infection (Alter, 2006). Among *HIV*-positive persons studied in Western Europe and the USA, chronic *HBV* infection has been found in 6 - 14% overall, including 4 - % heterosexuals, 9 - 17% of men who have sex with men and 7 - 10% of injection drug addicts. *HCV* infection was found in 25 - 30% of HIV-positive persons overall, 72 - 95% of injection drug addicts, 1 - 12% men who have sex with men and 9 - 27% heterosexuals (Alter, 2006). According to a Bulgarian study (Alexiev *et al*., 2017), there are 10.4% HbsAg/HIV co-infected persons, 51% of whom with *HBV* DNA-positive status, *HCV/HIV* co-infected persons in 25.6% with *HCV* RNA-positive status in 78.1%. Another study (Platt *et al*., 2016) indicates *HIV/HCV* co-infection in 2.4% of general population samples, 4% within pregnant women or heterosexuals, 6.4% in men who have sex with men, and 82.4% in injection drug addicts. In terms of *HBV* and *HCV* co-infection in the persons living with *HIV* based on serological assessments, the prevalence of infection appears to be much higher than in the general population. According to a study in Nepal (Ionita *et al.,* 2017), after investigation of patients openly living with *HIV*, *HBV/HIV* co-infections were documented in 4%, *HCV/HIV* co-infections - in 19%, and *HIV/HBV/HCV* co-infections - in 1%. Co-infection with both *HBV* and *HIV* exacerbates the negative effects and approximately 10% of the *HIV*-infected population have concurrent chronic hepatitis B (Thio, 2009; Kourtis *et al.,* 2012). *HBV* co-infection appears to have no impact on the progression of *HIV* to AIDS, but there are reports suggesting that *HIV* co-infection modifies the natural history of *HBV* infection, resulting in an increased percentage of persons with *HIV* becoming carriers of HbsAg. Similarly, *HIV* infection exacerbates *HCV* infection (Petty *et al*, 2014b). In our retrospective study, which includes 108 patients living with *HIV* infection, we received serological data for hepatitis B in 12 (11%), hepatitis B/C co-infection in 2 (1.9%), and hepatitis C in 6 (5.6%). Our region belongs to the higher-intermediate level of HBV endemicity that is why *HBV/HIV* co-infections are more common than *HIV/HCV* co-infections in patients living with *HIV*.

Syphilis is the most common co-infection in our living with *HIV* patients investigated - 24/108 (22.2%). In literature, the reasons for the rapid increase in syphilis among the people living with *HIV* are complex and include unsafe sexual practices. It is estimated that 20 -50% of men who have sex with men with syphilis have concurrent *HIV* infection. Today, syphilis in Western Europe and the USA is characterized by low-level endemicity, with concentration among sexually promiscuous subgroups, poor access to health services, social marginalization, or low socioeconomic status. The reasons for these outbreaks include changing sexual and social norms, interactions with increasingly prev-

alent *HIV* infection, substance abuse, global travel and migration (Paz-Bailey *et al.,* 2004; Truong *et al.,* 2006; Zetola *et al.,* 2007; Farhi *et al*, 2010). Syphilis may present with non-typical features in the *HIV*-positive patients. There is a higher rate of symptomless primary syphilis and proportionately more *HIV*-positive patients present with secondary disease. Secondary infection may be more aggressive and there is an increased rate of early neurological and ophthalmic involvement (WA and Lightman, 2004). Our data is in concordance with these findings in literature and we agree with the importance of unsafe sexual practices in heterosexuals, in man who have sex with men, and in sexually promiscuous persons. There is a reason to test all the *HIV*-positive persons for syphilis. Chronic *CMV* infection has been associated with immunosenescence and immunoactivation in the general population. In *HIV*-infected people, *CMV* co-infection has been proposed as a key factor in sustaining immune activation, even in individuals with a controlled HIV load (Lichtner *et al.,* 2015). *CMV* is responsible for the most common viral opportunistic infections in persons with *HIV*/AIDS. Clinical disease due to *CMV* has been recognized in up to 40% of patients with advanced *HIV* disease. The most common presentation is retinitis, although colitis, esophagitis, pneumonitis and neurological disorders are also reported frequently. A Canadian study (Kim *et al.,* 2006) presents *CMV* seropositivity rate in 93% of 2655 investigated *HIV*- infected patients, of whom 169 (6.4%) developed *CMV* disease. In 166 patients, disease was attributable to reactivation of latent *CMV* infection, whereas in 3 patients, disease developed following documented *CMV* seroconversion. Out of the 108 patients living with HIV infection in our study, we received serological data for *CMV* IgG seropositivity in 97% and the estimated seroprevalence is higher than in regional population. In the general North-Eastern Bulgarian population, the median seropositivity is 78.4% (Stoykova *et al.,* 2016). Serological data of reactivation of *CMV* infection we found in 21 patients (19.4%) with anti *CMV* IgM positivity. According to data (Lichtner *et al.,* 2015), *HIV*-positive patients with *CMV* IgG positivity at baseline were more likely to develop a severe non-AIDS-defining event / non-AIDS-related death. In this study *CMV* prevalence according to anti *CMV* IgG presence is 83.3% and the authors support a potential independent role of *CMV* co-infection in vascular degenerative organ disorders in *HIV*-infected subjects.

## Conclusion

Despite several advances in the understanding of the interaction between *HIV* infection and syphilis, *HBV, HCV, CMV* achieved during the past few years, the clinical treatment of co-infected patients remains challenging and will require innovative public health strategies to control. *HIV* infected patients in our study most commonly had co-infection with syphilis and clinicians must educate patients and counsel them in sexual risk reduction. *HIV* positive patients co-infected with *HBV, HCV, CMV* have a higher risk of progression to chronic liver disease than those with monoinfections.

More severe *HIV* symptoms may not appear for 10 years or more after the initial *HIV* infection as in our newly diagnosed patients. People exposed to the virus should get tested immediately and a follow-up test depending on the initial time of exposure. We believe our data could help health professionals with the most common clinical manifestations of *HIV* infection.

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