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THE CHRONIC INFLAMMATORY STATUS IN PATIENTS WITH HIV INFECTION

Clara Rodriguez de Castro Zaloña, Daiva Vėlyvytė
Lithuanian University of Health Sciences

Background and objectives

Currently, Human immunodeficiency virus (HIV) positive patients undergoing treatment have an expected lifespan moderately shorter than non-HIV individuals. Consequently, the effects of ageing on HIV positive individuals have begun to be apparent. The appropriate management of comorbidities has increasingly become an integral part of the overall management of individuals living with HIV. Potential contributors to comorbidity pathogenesis include a higher prevalence of recognized risk factors, antiretroviral therapy (ART)-exposure and toxicity, HIV itself as well as immune dysfunction/dysregulation and chronic immune activation/inflammation, associated with HIV or other co-infections (e.g. cytomegalovirus (CMV), Hepatitis C virus (HCV)). This inflammation is especially obvious in older adults with chronic, well-treated HIV infection; thus, patients aged more than 50 years may undergo pathologies that normally affect much older individuals. The chronic inflammation and the persistent immune activation can be displayed in HIV positive patients related to the premature ageing, development of cardiovascular diseases and neurocognitive disorders. The mechanism(s) underlying the immune activation and chronic inflammation are poorly understood, but assumedly resulting from both direct and indirect effects of HIV.

In the primary infection appears that the immune system, at the level of the intestine, is permanently damaged, resulting in bacterial translocation, therefore this situation causes a persistently activated inflammatory and immunological state.

1. To create a literature review to update the knowledge of the mechanisms that maintain a situation of sustained immunological activation with a continued inflammatory activity in HIV patients, which may explain the early onset of different pathologies in HIV-infected individuals that typically affect the elderly.
2. To characterize markers that can help in the early diagnosis of damage in different affected organs.
3. To describe different pathologies triggered by the persistent inflammation and immune activation at the metabolic, cardiovascular, neurological, renal, hepatic and osseous levels.

Material and research method used

• Search strategy: Data bases of PubMed, Cochrane Library Plus, OVID and UpToDate were used.

• Period covered: last 10 years (2007-2017/2018).

• Study selection: articles obtained as full text were assessed, and those abstracts that did not focus on the topic were excluded.

• 1360 original articles and reviews were obtained, following the study selection 201 references were selected and analyzed.

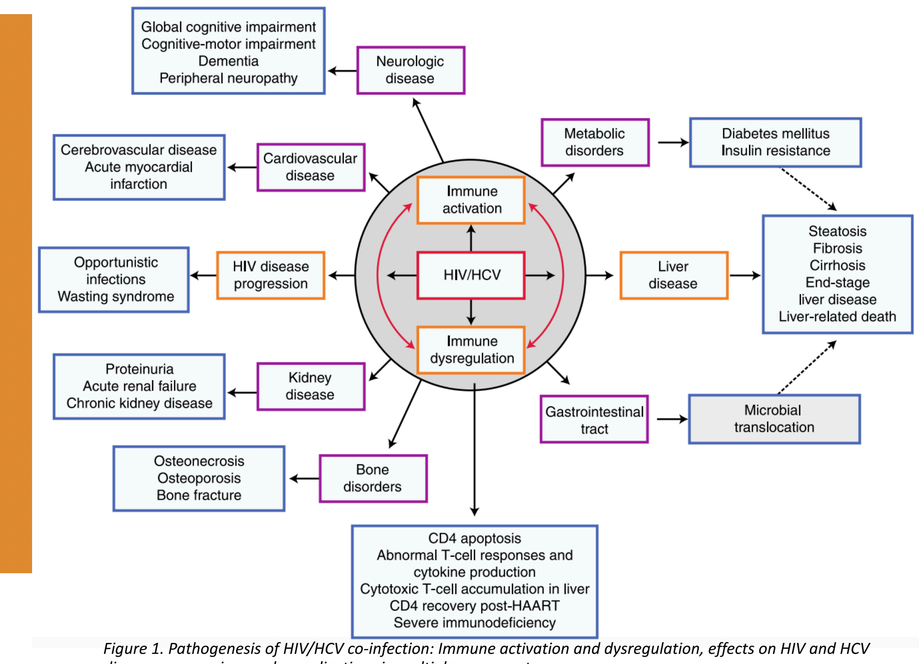

Figure 1. Pathogenesis of HIV/HCV co-infection: Immune activation and dysregulation, effects on HIV and HCV disease progression, and complications in multiple organ systems.

Findings/ results

• HIV is characterized by a persistent immune activation and inflammation, that combined antiretroviral therapy (cART) partially improves.

• cART is unable to fully control the viral replication. Moreover, has multiple side effects that help in the development of different pathologies occurring in the HIV population; however, its benefits surpass them, therefore, we continue using ART as the main treatment.

• Not only the cART takes part in the development of various disorders in the multiple systems, but also the HIV infection itself, the persistent inflammation and immune activation and its consequences.

• Gut-associated lymphoid tissue (GALT) is affected since the first days of infection, which leads to a microbial translocation within the intestinal tissue – playing a major role in the maintenance of the chronic immune inflammation and activation state.

• Other factors inducing the persistence are:

- Chronic activation of immune cells leading to the exhaustion of the immune system and release of proinflammatory mediators.
- Presence of co-infections: opportunistic (mainly CMV) and Hepatitis B virus (HBV)and HCV.
- Presence of reservoirs.

• Persistent immune activation releases proinflammatory cytokines which alter adipose tissue that favours metabolic disorders.

• HIV causes early cognitive and cerebral ageing.

- The use of cART prevents HIV-associated dementia (HAD), and is also associated with a marked improvement of HIV replication in the cerebrospinal fluid (CSF), decreased immune activation and neuronal damage.

• Renal pathology is caused by:

- Direct action of the virus (HIV-associated nephropathy (HIVAN), HIV immune complex disease of the kidney (HIVICK)).
- Associated to other co-infections (HCV, HBV).
- Certain antiretroviral drugs, especially Tenofovir in its Tenofovir disoproxil fumarate (TDF) form.

• Mortality due to liver disease is the most frequent in HIV patients:

- Direct action of the virus (HIV-associated nephropathy (HIVAN), HIV immune complex disease of the kidney (HIVICK)).
- It is characterized by its association with other co-infections (especially HCV).
- Emerging problem: Non-alcoholic fatty liver disease (NAFLD)/ Non-alcoholic steatohepatitis (NASH), caused by metabolic disorders, microbial translocation and systemic inflammation. Early diagnosis and treatment could reverse this trend.

• Increased prevalence of low Bone mineral density (BMD) and fractures in HIV patients.

- It is well known that HIV infection is associated with a high bone “turnover state”, and with increased markers of both resorption and formation. There is a "catabolic window".
- cART is one of the associated factors: during the first 2 years after its start there is a 2-6% bone mass loss.

Conclusions and recommendations

• The notion of HIV as an infectious disease is changing to that of inflammatory disease.

• Despite the suppression of viral replication offered by cART, which has led to a greater longevity in infected HIV patients, they don’t age as the general population. As HIV patients age, the consequences of the HIV infection become apparent with the development of the persistent inflammatory and immune activation syndrome.

• The early initiation of cART has shown a decrease in the immune activation and inflammation.

• Needs to be kept in mind that the cART:

- does not eradicate the virus
- does not prevent a continuous low level of replication
- does not impede the persistence of the immune activation
- does not restore the GALT, therefore, the microbial translocation persists.

• However, the cART has achieved great goals in improving the health and quality of life of infected patients.

• The research should be directed to establish the immunopathology of this chronicity.

• HIV is not a controllable chronic disease.

Keywords

"HIV and inflammation", "HIV and immune and activation", "HIV and inflammatory and markers", "HIV and cardiovascular and disease", "HIV and neurocognitive and disorder", "HIV and premature and ageing", "HIV and renal (or kidney) and disease", "HIV and hepatic (or liver) disease", "HIV and metabolic and disease ", "HIV and bone and disease".