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HIV/HBV coinfection: double trouble? Retrospective study outlining its negative synergistic effect.

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Resumo

A prevalência de infeção pelo vírus da hepatite B (VHB) é de 7,4% nas pessoas que vivem com infeção pelo vírus da imunodeficiência humana (VIH), com percentagens maiores em países em vias de desenvolvimento, nomeadamente na região da África Sub-Sariana de acordo com a Organização Mundial da Saúde (OMS). A coinfeção VIH/VHB está associada a um aumento do risco de morte relacionada com o fígado, comparativamente a doentes monoinfetados pelo VHB. Este risco é reduzido usando terapia anti-retroviral que tem atividade contra ambos os vírus. Existe um número reduzido de registos relacionados com a prevalência e efeitos clínicos desta co-infeção. Consequentemente, o autor decidiu investigar a informação disponível sobre esta t´pico e descrever uma coorte de pacientes com coinfeção VHB/VIH, com seguimento médico no Hospital Professor Doutor Fernando Fonseca (HFF) em Portugal, um contexto com um número particularmente elevado de migrantes provenientes da África Sub-Sariana

O autor compilou informação recente e disponível acerca desta co-infeção. Para além disto, uma coorte de doentes co-infetados do HFF foi descrita, retrospetivamente, analizando vairáveis sociodemográficas, caracterizando ambas as infeções, descrevendo os tratamentos e demonstrando resultados clínicos e baseados em scores de fibrose hepática não invasivos. Adicionalmente, aferiu-se a prevalência de coinfeções por outros vírus hepatotrópicos. Para medicão dos resultados de fibrose, foram usados dois scores internacionalmente reconhecidos, aspartate aminotransferase to platelet ratio index (APRI) e o Fibrosis-4 index (Fib-4).

Os resultados revelaram que regimes terapêuticos baseados em Tenofovir foram eficazes a atingir estabilidade clínica. Além disto, os scores de fibrose mostraram uma diminuição no seu valor ao longo do tratamento. A troca de fármacos entre regimes terapêuticos baseados em Tenofovir Disoproxil fumarato (TDF) para regimes baseados em Tenofovir Aladenamida mostrouser segura em termos de outcomes clínicos.

Palavras-chave:VIH;HBV;coinfeção;sinergia;Tenofovir

Abstract

There is a prevalence of 7.4% of Hepatitis B Virus (HBV) infection in people living with Human Immunodeficiency Virus (HIV), with higher rates in developing countries, namely, sub-Saharan Africa according to the World Health Organization. HIV/HBV coinfection is associated with an increased risk of liver-related mortality, compared with patients with HBV infection alone. This risk is lowered by using antiretroviral therapy that has activity against both viruses. There is underreport of HIV/HBV coinfection prevalence and clinical outcomes. Consequently, the author decided to investigate accessible information on this subject and describe a cohort of patients with HIV/HBV coinfection, under medical follow-up in Hospital Professor Doutor Fernando Fonseca (HFF), Portugal, a setting with a particularly elevated number of migrants from sub-Saharan Africa.

The author compiled recent and available information regarding HIV/HBV infection. In addition, cohort of co-infected patients from HFF was described retrospectively analyzing sociodemographic variables, characterizing both infections, describing treatment, clinical and non-invasive fibrosis scores outcomes and assessing the prevalence of additional coinfections by other hepatotropic viruses. To measure fibrosis outcomes, two internationally recognized scores were used, Aspartate aminotransferase to platelet ratio index (APRI) score and Fibrosis-4 index (Fib-4).

Results revealed that Tenofovir based therapy was effective in achieving clinical stability. Moreover, fibrosis scores showed a decrease in value, over the course of therapy. Drug switch from Tenofovir Disoproxil Fumarate (TDF)-based therapy to Tenofovir Alafenamide (TAF)-based therapy appeared to be safe in terms of clinical outcomes.

Key words: HIV; HBV; coinfection; synergy; tenofovir

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List of Abbreviations and Acronyms

3TC – Lamivudine

AIDS - Acquired Immunodeficiency Syndrome

APRI - AST to platelet ratio index

ART – Antiretroviral therapy

AST – Aspartate aminotransferase

AZT – Zidovudine

CT – Computed tomography

CXCL10 - C-X-C motif chemokine ligand 10

EASL - European Association for the Study of the Liver

EFV – Efavirenz

Fib-4 - Fibrosis-4 index

HAV - Hepatitis A Virus

HBeAg - Hepatitis B e-Antigen

HBsAg - Hepatitis B surface-Antigen

HBV – Hepatitis B Virus

HCV - Hepatitis C Virus

HDV - Hepatitis Delta Virus

HFF – Hospital Professor Doutor Fernando da Fonseca

HIV – Human Immunodeficiency Virus

IL-8 – Interleukin-8

LPS – Lipopolysaccharides

MRI – Magnetic resonance imaging

MSM – Men who have sex with men

PNV – Plano Nacional de Vacinação

PPAR-γ - Peroxisome proliferator-activated receptor-γ

PWID – People who inject drugs

TAF - Tenofovir Alafenamide

TDF - Tenofovir Disoproxil Fumarate

TRAIL-R2 – Tumor-necrosis factor-related apoptosis-inducing ligand receptors-2

UNICEF – United Nations Children's Fund

US – Ultrasound

VpR – Viral protein R

WHO – World Health Organization

Introduction

Coinfection of HIV (Human Immunodeficiency Virus) and HBV (Hepatitis B Virus) presents a formidable challenge for global public health. Both viruses, individually notorious for their impact on human health, pose a unique and intricate threat when coexisting within the same host. This thesis intends to delve into the multifaceted dynamics of HIV and HBV coinfection, describing the epidemiology, synergistic interactions, and clinical implications of coinfection, as well as treatment efficacy with a brief literature review of the topic. Moreover, it describes a retrospective cohort study of patients in Hospital Professor Doutor Fernando Fonseca (HFF), outlining the epidemiology of this infection in the context of Portuguese society.

HIV and HBV, both bloodborne pathogens, share common modes of transmission, including unprotected sexual intercourse, needle sharing among intravenous drug users, and mother-to-child transmission during childbirth (WHO, 2024). As a result, the co-occurrence of these infections is not uncommon, particularly in regions with high prevalence rates of both viruses, like Sub-Saharan Africa (Mohd, Sami, Khan, & Khan, 2023). One study found that in the United States and Europe, 50% of individuals infected with HIV have a history of exposure to HBV, highlighting a substantial correlation between these two viruses (BH., 2007).

To draw reliable conclusions about the prevalence, distribution, and impact of HIV and HBV coinfection, there is an unequivocal need for robust epidemiological data. Current gaps in data collection and reporting hinder our ability to formulate effective public health strategies. This study advocates for an intensified focus on gathering comprehensive epidemiological data, emphasizing the necessity for standardized reporting practices and implementation of surveillance programs. For this, a description of a retrospective cohort of 26 people will be presented. By addressing this data deficiency, the thesis aims to enhance the precision of coinfection understanding and pave the way for more targeted interventions.

As the landscape of HIV and HBV coinfection unfolds, it becomes evident that a holistic and multidisciplinary approach is imperative. This thesis aims to contribute to the existing body of knowledge by examining the intricate web of interactions between HIV and HBV, shedding light on the clinical implications and treatment challenges. By unraveling the complexities of this coinfection, it strives to pave the way for more effective strategies to mitigate infection impact on individuals and communities worldwide.

Literature Review

Epidemiology

The World Health Organization (WHO) states a prevalence of 7.4% of HBV infection in people living with HIV (WHO, https://www.who.int/news-room/fact-sheets/detail/hepatitis-b, 2023). A meta-analysis in 2020, (Steve Leumi, 2020) including more than 800 000 people living with HIV, estimated a co-infection prevalence of 8.4% in this population. This study included data from different centers globally and allowed to compare prevalences as high as 12.4% in Central and West Africa and as low as 5.1% in Latin America and Caribbean. Asian data, however, has extremely big ranges of prevalence. In China, prevalences range from 4.5% to 12.5% in individuals with HIV, depending on the region (Mohd, Sami, Khan, & Khan, 2023), showing the need for better epidemiological studies.

In countries where HIV prevalence is high, there is more probability of higher percentual co-infection, outlining the same routes of transmission. Moreover, the rates of coinfection can easily be linked to the level of Human Development Index: lowest scoring countries have a coinfection percentage of 10.4%, whereas in the very highly developed nations this number decreases to 6.6% (Steve Leumi, 2020). This phenomenon could be explained by the association of this Index to weaker health systems, lower levels of education and lower income.

It is also worth noticing the different percentages of coinfection depending on transmission type subgroups. The prevalence of this condition is about 16% within sex workers, a twofold increase compared to the global prevalence in people living with HIV; it reaches approximately 14% among injection drug users, while among Men who have Sex with Men, the prevalence is comparatively lower at 12.4% (Steve Leumi, 2020).

The prevalence of this co-infection over the years has been stable (Steve Leumi, 2020). However, this data must be interpreted with caution since both infections are chronic. Thus, the number of infections might be inflated by this mechanism but also

balanced by the fact that people with co-infection might die earlier, leading to stability overtime. Thus, studies should be based in incidence levels; that way they might be a lot more informative about disease progression in society.

Hepatitis B vaccine has been distributed globally, particularly in children less than five years old by organizations such as United Nations Children's Fund (UNICEF) and WHO. Hepatitis B vaccine has been available since 1982 (UNICEF, 2024). According to WHO, the vaccination initiative started in Africa in 1995, reaching in 2019 a coverage rate of 77%. Globally, this coverage was, in 2019, at 86%. This vaccine was introduced in Plano Nacional de Vacinação (PNV), the national Portuguese vaccination initiative, in 1995 (SNS24, 2023). Today, every newborn in Portugal is offered this method of passive prevention in a 3-dose schedule at birth, 2 months, and 6 months of age.

In Figure 1 we can see the impact this vaccination has had in infection incidence as well as related deaths.

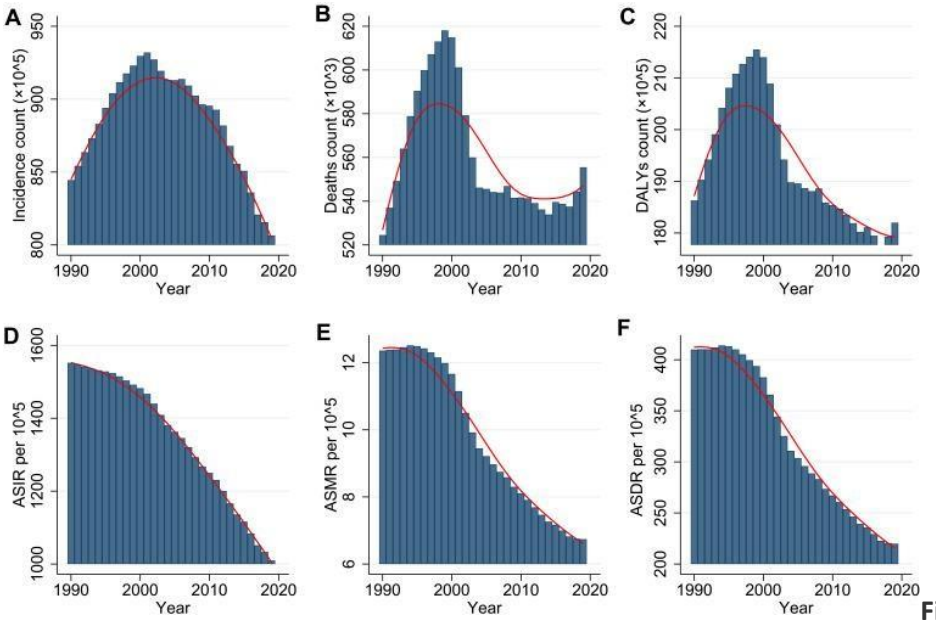

Figure 1

Abbreviations: DALYs, disability adjusted life years; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASDR, age-standardized DALYs rate.

Zhang C, Liu Y, Zhao H, Wang G. Global Patterns and Trends in Total Burden of Hepatitis B from 1990 to 2019 and Predictions to 2030. Clin Epidemiol. 2022 Dec 14;14:1519-1533

Pathophysiology of coinfection

The pathophysiology of this co-infection has been a particularly controversial topic among investigators because of the uncertainty related to it. To this day, there is no single good mechanism describing the whole synergy between HIV and HBV (Cheng Z, 2021). There are few data about the interaction between HIV and HBV proteins (MK., 2015). There are, nonetheless, good hypotheses regarding their effects in the hepatic environment.

To understand the effects of their combination, we should firstly visit the immunology behind HBV infection. The main response to HBV is based in a combination of humoral and cellular immunity, antibodies and T cells. It has been shown that hepatocytes in which HBV is replicating can either enter apoptosis with cytotoxic mechanisms or eliminate the virus through cytologic sparing mechanisms (Rehermann B, 2005) (Giovanna Fattovich, 2008). There is a possibility of spontaneous viral clearance in chronic hepatitis B of around 2% each year that is directly related to the levels of HBV-specific T cells in circulation (Rehermann B, 2005).

The main proposal for the mechanism of HIV/HBV synergy is multifactorial (Singh KP, 2017). There is direct infection of HIV in multiple cells in the liver, namely, Kupffer cells, hepatocytes, and hepatic stellate cells, contributing to local tissue destruction (Singh KP, 2017).

Furthermore, it is proposed that HIV infects enterocytes, increasing microbial translocation and LPS (lipopolysaccharides) levels in portal and systemic circulation. LPS binds to Toll-like receptor 4 and initiates a local inflammatory response based on native immunity that modulates fibrosis (MK., 2015).

It was also noticed that HBV DNA and fibrosis levels were correlated with lower CD4+ cell counts, proposing that a weaker T cell response in the onset of HIV infection leads to the progression of liver disease (MK., 2015).

At the molecular level, there are many proposals made regarding HIV proteins. Glycoprotein gp120, a superficial HIV protein, has been linked to upregulation of tumor

necrosis factor-related apoptosis-inducing ligand receptors-2 (TRAIL-R2), inducing apoptosis of hepatocytes (Cheng Z, 2021) (MK., 2015). This same protein has also shown to increase levels of Interleukin-8 (IL-8), a leucocyte chemotactic substance, capable of maintaining a pro-inflammatory environment and inducing fibrosis. IL-8 levels were positively correlated to liver damage (Cheng Z, 2021). Another protein, viral protein R (VpR), from HIV is known to reduce expression of peroxisome proliferator-activated receptor-γ (PPARγ), crucial in lipid metabolism and fibrogenesis. The inflammatory hepatocytes secrete C-X-C motif chemokine ligand 10 (CXCL10) that can accelerate liver disease. Elevated levels of CXCL10 were found in HBV/HIV coinfection but not in HBV mono-infected patients.

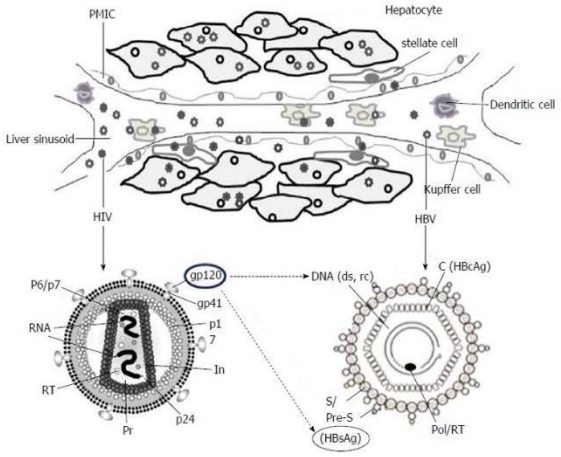

Figure 2

Parvez MK. HBV and HIV co-infection: Impact on liver pathobiology and therapeutic approaches. World J Hepatol. 2015 Jan 27;7(1):121-6

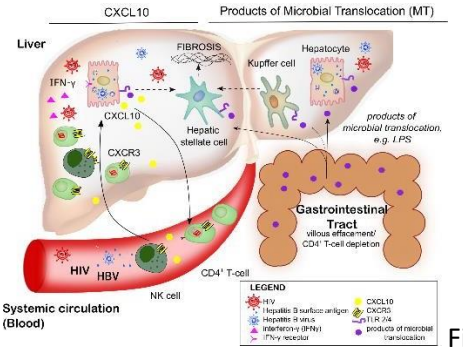

Figure 3

Singh KP et al. Intrahepatic CXCL10 is strongly associated with liver fibrosis in HIV-Hepatitis B co-infection. PLoS Pathog. 2020 Sep 8;16(9

Transmission

HIV and HBV share mechanisms of transmission, justifying the coinfection prevalence already mentioned. The spread of these conditions is mainly driven by 2 modes of transmission: vertical (mother-to-child transmission) or horizontal (parenteral or sexual transmission).

HIV transmission is mostly related to unprotected sexual intercourse. The probability of acquiring this infection depends on the type of sexual exposure and if the person is receptive or insertive. Receptive behavior is connected to higher probability of contracting the infection. Anal sex compared to penile-vagina intercourse is also linked to increased chances of transmission (Shaw GM, 2012). However, it is proposed that most transmissions occur through vaginal-penile sex, making about two thirds of HIV cases worldwide (Shaw GM, 2012). More recent data shows that in Europe, United States and Brazil, young MSM people are disproportionately represented in new infections, and the number has been rising (Govender RD, 2021). No country managed to reach their 2020 target (Govender RD, 2021).

Mother-to-child in utero transmission is stated to be from 25-30% by WHO, however, there is a risk associated with breastfeeding, increasing the overall chance of the mother transmitting the infection to the child.

Blood contact, in needle sharing, for example, accounts for about 10% of total cases (Shaw GM, 2012).

HBV transmission varies by region. In countries with a high incidence of HBV, the most important mode of transmission is mother-to-child. This happens because there is no prenatal care with screening for this infection and no passive or active immunization of the newborn. This type of transmission happens mostly during birth, but it can also occur *in utero*, despite lower probability. In developed countries the main mode of transmission is sexual or parenteral and most infections only start in adulthood. With this data in mind, it can be affirmed that the higher the carrier rate of HBV in a certain population, the higher

the chance of being infected earlier in life. It is also worth noting that people infected without any known risk factor were linked with poorer economic status (Eng-Kiong Teo, 2023).

With the types of transmission well described the main risk factors for HBV and HIV infection are having multiple sex partners without using protection, sharing used needles and being healthcare workers especially in areas with higher infection prevalence, for example. Populations at particular risk are sex workers, men who have sex with men, persons who inject drugs, incarcerated people, and people with lower levels of income (Eng-Kiong Teo, 2023).

Clinical features/Laboratory results

This section will focus on the synergistic effects of the two viruses instead of describing the clinical features of each infection. Thus, the effects that HIV has on HBV infection and vice-versa will be described. The impact of HIV on HBV-induced hepatitis is significantly different from the impact that HBV infection might have on HIV infection progression.

1. The effect of HIV in the progression of chronic liver disease

   Around 10-15% of coinfected people develop chronic hepatitis B, compared to 5% in HBV monoinfection, showing lower levels of HBV elimination (Shahriar S, 2022). In these coinfected patients, alanine aminotransferase levels are lower and Hepatitis B e-Antigen (HBeAg) decrease occurs at a lower rate compared to HBV carriers (Gilson RJ, 1997), showing higher levels of infectivity. One large prospective study described that HIV viral suppression at 6 months reduced the risk of liver complications in HBV-HIV co-infected patients (L., 2021).

2. The effect of HBV in the progression to Acquired Immunodeficiency Syndrome (AIDS)

   This topic in specific is, to this day, still very controversial. There are studies showing that there is, in fact, an acceleration of the process of AIDS development (L., 2021) .

However, there are also studies refuting this theory, saying that it is just a lead time-bias (Gilson RJ, 1997). The information in this topic is limited, and so it is difficult to draw a good conclusion.

The chances of developing immune reconstitution inflammatory syndrome were also higher in coinfected patients. This might be due to the inflammatory response to high levels of Hepatitis B surface-Antigen (HBsAg) (EASL, 2017).

All HBsAg positive patients must be screened for HIV (EASL, 2017). The same way, HIV positive patients must be screened for HBV infection (EACS, 2023). Additionally, screening for other hepatotropic infections, like Delta Hepatitis Virus (DHV), Hepatitis C Virus (HCV) or Hepatitis A Virus (HAV). Other causes of liver disease must also be screened because of the risk of potentiating effects (EACS, 2023).

Liver Fibrosis Evaluation

Liver Fibrosis is one of the obvious complications of coinfected patients. To evaluate this variable, there have been developed different tools throughout time to better estimate the impact of hepatotropic infections in clinical outcomes. To this day, three main techniques are used: histologic evaluation, imaging, and serologic biomarkers (Horowitz JM, 2017).

Traditionally, the determination of hepatic fibrosis was made using liver biopsy. Besides providing a particularly good estimation of disease progression, it was key to determining the etiology of the disease. However, it is not the optimal method for serial evaluations because of patient acceptance and risks. (Horowitz JM, 2017).

Imaging methods can be made using ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). The most reliable techniques are US elastography and MR elastography. However, these methods are not readily available in every center, making the serial evaluation harder (Horowitz JM, 2017).

To overcome these limitations, there have been created multiple scores based on laboratory levels of certain enzymes to better estimate the progression of liver fibrosis non-

invasively. Two examples of these scores are AST to platelet ratio index (APRI) and Fibrosis-4 index (Fib-4). APRI score showed 93.8% sensitivity and 72.4% specificity in diagnosing liver cirrhosis. These results were, unfortunately, worse for diagnosing earlier stages of liver fibrosis (65% sensitivity and 78% specificity) (El Serafy MA, 2017). In the case of Fib-4 score, it showed sensitivity values of 65.4% and specificity values of 73.6% for significant fibrosis (Xiao G, 2015). None of these have been validated to specifically HIV/HBV coinfection.

Treatment

HBV treatment may rely on monotherapy, but HIV treatment (antiretroviral therapy, ART) must be based on combined therapy to prevent HIV drug-resistance emergence.

Treatment of HIV/HBV coinfection has clear Guidelines by European Association for the Study of the Liver (EASL) and European AIDS Clinical Society (EACS). Both HIV and HBV have indication for treatment start, irrespective of each infection staging (EACS, 2023) (EASL, 2017).

Some antiviral drugs have activity against both virus, simultaneously, so they should be included in therapeutic regimen, namely the nucleoside analogues: Tenofovir Disoproxil Fumarate (TDF) or Tenofovir Alafenamide (TAF), with TDF having level I of evidence and TAF II-1 (EASL, 2017). Comparing to TDF, TAF has greater levels of plasma stability, enhanced hepatic delivery and allows lower circulating levels of tenofovir, that translates into potential differences in safety profile. There is still lower-grade evidence with TAF-containing ART because of studies with a petite population, but it has been shown that it might have the same virological efficacy with better renal and bone-related outcomes (estimated glomerular filtration rate and bone mineral density) (EASL, 2017). Two phase-3 comparative studies showed that switching from TDF to TAF in patients with HBV was safe and resulted in improvements in renal and bone safety parameters (Young-Suk Lim, 2023).

Emtricitabine and Lamivudine, other nucleoside analogues, both show antiviral activity against both viruses. However, neither can be used as monotherapy for HBV

treatment, because of high rates of resistance induction (lower genetic barrier) (Cheng Z, 2021).

Entecavir, another nucleoside analogue with activity against HBV, is the best alternative when there is an absolute contraindication for TDF/TAF use, in combination with other drugs as ART for HIV.

Interferon-gamma treatment has mostly been abandoned because of better options like those described above. It demonstrated effective control over HBV levels, but it lacked anti-HIV action. (Cheng Z, 2021)

In the future, there might be new other options:

- CRV-431, a non-immunosuppressive cyclophilin inhibitor - cyclosporin A analog, has shown promising results in combination with tenofovir exalidex, a prodrug of tenofovir. It has action in transgenic mice HbsAg levels and HBV DNA as well as HIV RNA. Liver fibrosis was ameliorated. It is now in a clinical trial to assess safety (Cheng Z, 2021);
- Vesatolimod/GS-9620, an antagonist of Interleukin-7 receptor, has proven outstanding anti-HBV performance, even suggesting that it could help the immune system eliminate the virus by inducing the accumulation of CD8+ T cells and B cells in the liver. It has also shown that it is a good inducer of latent HIV, helping the immune system to recognize this infection and improving its clearance. Because of this dual activity, it has been proposed that it can be a beneficial drug in HBV/HIV coinfection (Cheng Z, 2021);
- Pembrolizumab, a checkpoint inhibitor that targets PD-1, that already proved its safety. Since it enhances the immune system response, few studies have been done with this drug because of the theoretical risk of immune reconstitution Inflammatory syndrome. The evidence with this molecule is still controversial, but some studies have suggested a good anti-HIV activity (Cheng Z, 2021).

It is important to mention the risk of immune reconstitution inflammatory syndrome that might be associated with any of the therapeutic strategies described above. It is

suggested that up to 25% of coinfected patients might appear with HBV flares, showing raised levels of alanine aminotransferase, after the start of ART. Higher levels of basal HBV DNA were linked with the risk of developing this condition (Cheng Z, 2021).

HBV treatment should be maintained chronically since there is high risk of hepatic flares and decompensation following HBV reactivation hepatitis. Anti-HBV therapy may be stopped cautiously after confirmed HBsAg-HBsAb (Hepatitis B surface-antibody) seroconversion. ART for HIV should be continued indefinitely, without interruption (EASL, 2017).

Prognosis

Today, none of these infections can be fully cured. Because of this, life-long treatment is proposed. However, in the specific case of HBV, there is a possibility that the disease is "functionally cured." This implies the loss of HBsAg and undetectable levels of serum HBV DNA. However, this only happens in about 1-3% of infections treated with nucleoside analogs. (Gopalakrishna, 2024).

Coinfected patients have a general mortality rate up to eight times higher than those singly infected with HIV. Furthermore, mortality associated with hepatopathy resulting from hepatitis B has notably risen since the introduction of highly active antiretroviral therapy for HIV, since patients now have fewer opportunistic infections and live longer. Earlier research suggests that coinfection leads to a liver-related mortality rate 19 times higher than that of singular infections by HBV. This mortality rate is higher in individuals with HIV and lower CD4+ T-cell counts (Shahriar S, 2022).

Liver-related mortality in coinfected patients was only 8 times higher than in those monoinfected with HIV since more people with HIV already die of liver-related complications (Thio CL, 2002).

Methods

Hospital Professor Doutor Fernando Fonseca is located in Amadora, a county with a peculiar demography. About 10% of the population has a foreign nationality and about 18% was born in another country (Amadora, 2024). These migrants come mostly from Portuguese speaking countries (Cape Verde, Angola, Mozambique, S. Tomé and Príncipe and Guinea Bissau), all located in Sub-Saharan Africa, where, as described before, prevalences of HBV and HIV infections are much higher than in European countries. As a result, the population served by this hospital exhibits a notably elevated frequence of these specific infections, rendering it a prime facility for researching these diseases.

A cohort of 26 HIV/HBV-coinfected patients with regular follow-up starting in 2013, 2014 or 2015 was conducted. 2013 was chosen as the starting year since it was when patient data started to be mostly computerized, making it more reliable and easily accessed. Patient's outcomes have been evaluated until 2023. With up to 10 years of office visits, an accurate description of treatment success or failure could be made.

The main outcome is the state of follow-up in 2023, with four options: under follow-up, stable; under Follow-up, with liver fibrosis evolution (can be because of therapeutic failure or bad treatment adherence), lost to follow-up or dead.

Data was collected and stored with pseudonymization.

For each patient data have been collected regarding their sociodemographic characteristics: age, gender, country of birth, race, and date of entrance in Portugal.

Regarding HIV infection, it has been gathered data on HIV type, date of diagnosis, country of diagnosis, context of diagnosis, basal, nadir and current CD4+ cell count (absolute and relative count), basal and current viral load, clinical staging (using 1993 revised classification system by Centers for Disease Control and Prevention) at diagnosis/evolution during follow-up, confirmed/probable transmission route, date of ART initiation, current ART treatment, data on treatment interruptions.

For HBV infection, data have been collected on date, country and context of diagnosis, basal and current HBV serology, basal viral load, basal and current APRI (AST to Platelet Ratio Index) and FIB-4 (Fibrosis-4) scores, current viral load, current HBV treatment and data on treatment interruptions.

Because of bias and eventual potentiating effects, data regarding other viral hepatitis: HAV, HCV and DHV, as well as presence of other causes for liver fibrosis, has been collected.

Results

Epidemiology

Our Study revealed that out of 26 patients only 5 of them were women. 27% were Portuguese while the rest of the population studied was mainly from Africa (Guinee-Bissau, Angola, Cape Verde and S. Tomé and Príncipe). Because of these places of birth, the main race was black, translating in 65% being African-Descendant.

The date of entrance in Portugal ranges from 1990 to 2010.

The mean age was 48.8 years old with an outlier of 78 years old.

HIV Infection Characterization

The vast majority of infections was by HIV-1. There were only 2 patients that presented with both HIV-1 and HIV-2, equally from Guinea-Bissau. Most infections were diagnosed in Portugal except for 3. The dates ranged from 1995 to 2015.

The Clinical Categories at the time of infection can be divided in: 13 cases in Stage A, 3 cases in Stage B, in 9 Stage C and 1 unknown stage. Transmission Routes were either Heterosexual (62%), Unknown (23%), PWID (12%) or Homosexual (3%).

3 of the patients did not have an initial CD4+ cell count because of diagnosis in 1990's and the data were lost. Nonetheless, the nadir CD4+ cells count with <100 were 8 patients, 100-200 were 8 patients, >200 were 7 patients. The median was 246 CD4+, with a minimum of 2 and a maximum of 582. The CD4+ cell count at time of diagnosis was basically the same as the nadir except for 7 patients that did not start ART because of the old guidelines since they had levels of CD4+ above 500.

All the patients have at least 8 years of ART, depending on time of diagnosis.

The most recent viral load and CD4+ cell count was determined. Out of the 26, only 1 had a detectable viral load at 280 copies. No patients revealed levels of CD4+ below 200.

HBV Infection Characterization

The diagnosis of HBV infection was for the substantial majority of patients related to screening for Sexually Transmitted Infections in the scenario of HIV infection except for 2 patients, which was related to Acute Hepatitis. Because of this, the date of diagnosis correlates with the date of HIV infection in most patients.

Basal HBV DNA values showed a median of 79350 (n=14). The values ranged from 208 200 000 to undetectable (<4).

In terms of HBV infection evolution, 6 patients lost HBsAg, presenting as a functional cure, while the rest of the patients showed the same serological markers compared to the time of diagnosis. 4 patients did not have reevaluation of serological HBV status.

Other causes of Liver damage

We found that 6 patients were co-infected with DHV. Besides this, 4 patients had DHV as well as past HCV infection that was cured. 1 patient had past HCV infection without DHV infection that was also cured. No patient was found to have HAV, but 9 of them had positive serological immunization, 6 were negative for active infection or immunization and 11 patients did not have records. The records on HAV vaccination were also very insufficient. Only 4 patients had other causes for liver fibrosis and it was connected with high alcohol consumption. No patient was found to have hepatocellular carcinoma.

Every patient is under follow-up and stable, except for one death related to lost to follow-up followed by septic shock. There is also one patient that lost follow-up for the last 6 months only.

Therapeutic Strategies

The majority of patients started pharmacological therapy with Tenofovir-Disoproxil (TDF) based scheme (80%) and the other 20% with Lamivudine (3TC) based therapy as well as Zidovudine (AZT), and Efavirenz (EFV). The time of therapy initiation differed among patients based on the date of diagnosis. Most patients are now taking a Tenofovir-

Alafenamide based therapy (n=23). Of the remaining 3 patients, 2 are still taking a TDF based strategy and 1 with Lamivudine, Abacavir and Dolutegravir.

Liver Fibrosis Scores

APRI scores at the time of diagnosis showed a median value of 0.587, with a minimum of 0.223 and a maximum of 17.319. In 2023, APRI scores had a median value of 0.304, minimum of 0.089 and maximum of 0.724.

Fib-4 scores, in the beginning of the records, were 1.77 of median value. The minimum was 0.73 and maximum was 15.65. By the end of the study, the median was 1.37, minimum of 0.42 and maximum of 2.62.

Discussion

As we can see from the description above, even though this study was taken in Portugal, the vast majority of infections comes from Sub-Saharan Africa. This is easily explained by the historical laces Portugal established with these countries.

With this study, we can understand the importance of therapeutic strategies based of Tenofovir. Patients were mostly started on TDF and are now taking TAF and did not show any complications, highlighting the safety in drug switch. Moreover, throughout the 8-10 years of follow-up, none of the participants was clinically unstable, had opportunistic infections or progression of liver disease except for one death related to lost-to-follow up.

In terms of triple chronic infection, HIV/HBV/DHV without prior HCV infection, none of the patients has detectable levels of HBV DNA, HIV RNA or <200 CD4+ cell count, indicating that all of them were clinically stable.

The patient with prior HCV infection without concomitant DHV infection, had detectable values of HBV DNA.

None of the quadrupled infected patients (HIV/HBV/HDV with prior HCV infection) had HIV or HBV activity.

It is noteworthy to mention that every DHV infection had undetectable levels of DNA even though the patients only received treatment for HBV infection.

APRI and Fib-4 scores had an improvement throughout the follow-up. These reductions cannot be directly related to clinical outcomes but indicate that laboratory values of liver damage were generally lower after Tenofovir treatment.

To sum up, Tenofovir-based therapy managed to control clinically every patient. The hypothetical potentiating effects of concomitant hepatotropic infections did not worsen laboratory or clinical outcomes. Non-invasive fibrosis scores comparison showed a decrease in the probability of having liver fibrosis after Tenofovir treatment. It is also worth noting that data on HAV vaccination and immunization status was very insufficient, stressing the

need to better educate healthcare workers on the importance of screening and vaccinating for other hepatotropic viruses. The same can be stated for HBV vaccination condition that was very incomplete in the records, whether because the patient did not know, or because the physician did not register.

Conclusion

In conclusion, this thesis has delved into a comprehensive study and literature review focused on the intricate dynamics of HIV/HBV coinfection. Over the span of a decade, the research investigated 26 patients, offering valuable insights into the long-term outcomes and therapeutic strategies, particularly centered around Tenofovir therapy.

The paramount significance of this study lies in its contribution to the global understanding of HIV/HBV coinfection. The decade-long examination has provided insights into the sustained control of diseases, even among patients with an initial clinical category of C, showcasing the effectiveness of Tenofovir Disoproxil or Tenofovir Alafenamide therapy.

However, it is essential to acknowledge the limitations inherent in the study. The relatively small sample size of 26 patients warrants caution in generalizing the findings to a broader population. Moreover, the occasional irregular follow-up introduces a degree of uncertainty, emphasizing the need for more rigorous, standardized, prospective follow-up protocols in future studies.

As we navigate the complexities of HIV/HBV coinfection, the insights gained from this thesis underscore the need for ongoing research in this domain. While this study contributes significantly to the existing knowledge, there is a clear call to action for more extensive and diverse studies, encompassing larger populations and varied treatment regimens. The complexities surrounding this dual infection demand a multifaceted approach to further enhance our understanding and guide effective strategies for managing HIV/HBV coinfection on a global scale.

In wrapping up this thesis, it is my sincere hope that this work serves as a catalyst for continued research and fosters a deeper comprehension of HIV/HBV coinfection, ultimately contributing to improved patient outcomes and advancing the field of infectious diseases.

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