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ARTIGO DE REVISÃO / *REVIEW ARTICLE*

Prevenção da transmissão de VIH e de outras doenças infecciosas na era da terapia antirretrovírica

Prevention of HIV transmission and other infectious diseases in the era of antiretroviral therapy

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/ Resumo

Introdução: A terapêutica antirretrovírica permitiu um aumento não só da longevidade, mas também da qualidade de vida das pessoas que vivem com VIH. A implementação desta terapêutica teve um impacto significativo na saúde pública ao reduzir a transmissão materno-fetal e ao permitir níveis indetectáveis de VIH indicativos de protecção contra a sua transmissão. O uso desta terapêutica como profilaxia pré-exposição (PrEP) poderá agora alterar a evolução desta pandemia.
Objetivos: Este trabalho tem como objectivo abordar, por um lado, a utilização da PrEP e, por outro, as áreas da sexualidade, gravidez e vacinação em pessoas que vivem com VIH, com o objectivo de melhorar a sua qualidade de vida.
Métodos: Em Outubro de 2020, três peritos de diferentes áreas clínicas discutiram as principais estratégias de prevenção da infecção por VIH e de prevenção de comorbilidades infecciosas.
Resultados: PrEP e cuidados durante a pré-concepção, gravidez e parto foram abordados como estratégias de prevenção da transmissão da infecção por VIH. A vacinação e a gestão das infecções sexualmente transmissíveis foram abordadas como estratégias de prevenção de determinadas comorbilidades infecciosas
Conclusões: As recomendações específicas para cada uma das áreas abordadas são fundamentais para a melhoria da qualidade de vida da população portuguesa que vive com VIH.

Palavras-chave: Qualidade de vida; vírus da imunodeficiência humana; prevenção

/ Abstract

Introduction: *Antiretroviral therapy allowed not only the increase in longevity, but also an improvement of the quality of life of people living with HIV. Implementation of this therapeutic approach had a significative impact in public health, causing a reduction of mother-to-child transmission and allowing indetectable levels of HIV, indicative of protection against its transmission, to be reached. Utilization of this therapeutic approach as pre-exposure prophylaxis (PrEP) has the potential to alter the evolution of this pandemic.*

Aims: *This work aims to approach the use of PrEP and the sexuality, pregnancy and vaccination of people living with HIV with the goal of improving their quality of life.*

Methods: *In October 2020, three specialists of different clinical areas discussed the key strategies for prevention of HIV transmission and of infectious comorbidities.*

Results: *PrEP and precautions during preconception, pregnancy and childbirth were approached as strategies to prevent transmission of HIV-infection. Vaccination and management of sexually transmitted infections were approached as strategies to prevent transmission of certain infectious comorbidities.*

Conclusions: *The recommendations reported in this document, are essential for the improvement of the quality of life of the Portuguese population living with HIV.*

Keywords: *Quality of life, human immunodeficiency virus; prevention*

/ Introduction

HIV infection affects more than 39.6 million of people worldwide.[1] The development of antiretroviral therapies (ART) has promoted the increase in longevity of the population living with HIV, converting HIV-infection from a life-threatening disease to a chronic illness.[1-3] However, many might not have access to medication. In 2017, only 21.7 million people of the 37 million individuals living with HIV were receiving treatment and less than 18 million were virologically suppressed.[4] Additionally, the trajectory of the disease is variable and even carefully managed patients suffer consequences of lifelong medication.[1] Consequently, strategies to prevent HIV-transmission are still needed. One promising strategy is pre-exposure prophylaxis (PrEP), which is based on the consumption of antiretroviral medications by HIV-uninfected individuals to block HIV acquisition.[5] This strategy is of special importance for populations that have increased risk of contracting HIV due to factors such as their professional occupation or sexual behaviors.[5] The development of ART and PrEP also provided serodiscordant couples with the possibility of conceiving with reduced risk of viral transmission.[6] Moreover, ART coupled with specific pre-natal and delivery measures allowed the decrease of the mother-to-child transmission from 25-42% (without any prevention measures) to roughly 1%.[7,8]

Sexually transmitted infections (STI) are associated with higher transmission of HIV as contraction of these infections is indicative of risk behaviors that promote HIV acquisition.[9] Also, STIs promote the increase of HIV viral load in the genital tract, increasing the possibility of contracting HIV even under suitable ART.[9] Furthermore, individuals living with HIV have more probability of contracting STIs due to their impaired immune system, their frequent visits to medical settings and due to the fact that HIV has the same transmission route as other infectious pathogens like the human papilloma virus (HPV).[10] Thus, vaccination strategies that prevent these infections and even some cancers, can be beneficial.[10] Nevertheless, special care is needed for people living with HIV. Namely, the nature of the vaccines, the immunological status of the patients and the risk of naturally contracting the infection should be carefully considered, before recommending the administration of vaccines to people living with HIV.[11]

In this work, strategies to prevent HIV-transmission and to avoid the appearance of infectious comorbidities are presented, with the aim of improving the quality of life of the Portuguese population living with HIV. The work here presented constitutes the last part of a three-part expert review, which objective is to provide a complete overview of the strategies available to improve the quality of life of the Portuguese individuals living with HIV. Part I covered the current state-of-the-art on clinical management of the comorbidities that afflict people aged 50 years or older living with HIV, most commonly observed in the Portuguese healthcare system[12] and part II highlighted the key points on prevention, diagnosis and treatment of these comorbidities.

/ Methods

In October 2020, 2 physicians specialized in Infectiology and 1 physician specialized in Gynecology performed a literature review on pre-exposure prophylaxis, vaccination and on preconception, pregnancy, and childbirth of individuals living with HIV. A third infectious disease expert coordinated the work that was also overviewed by a scientific committee of three infectious disease experts. All authors contributed and were actively involved in the manuscript preparation and a consensus on the final text was reached in May 2021.

/ Prevention of hiv and transmission of infectious comorbidities

Pre-exposure prophylaxis and sexually transmitted infections

Pre-exposure prophylaxis (PrEP) was recommended by the World Health Organization in 2012[13] and became available in Portugal in 2017,[14] due to the observation that some antiretrovirals, taken in a prophylactic manner, significantly reduced the risk of infection with HIV.[13] This therapeutic approach is advised for people at risk of acquiring HIV infection. In Portugal, people at risk were defined as people that had sexual interactions without consistently using condoms with partners that might be infected in the last 6 months, people that have an HIV-infected partner, which is not retained in care or undergoing suppressive ART, people who consume psychoactive substances during sexual interactions with the previously mentioned types of partners, people who use intravenous illicit drugs, people that had one or more sexually transmitted infection (STI) in the last 6 months, people that were prescribed non-occupational post-exposure prophylaxis in the last 6 months, and serodiscordant couples in pre-conceiving or pregnancy states.[15] Clinical monitoring should be performed routinely with a basal evaluation performed in the fourth week after starting PrEP and quarterly evaluations afterwards.[16] PrEP usually consists of tenofovir disoproxil fumarate (TDF) together with emitricitabine (FTC) in a continuous or intermittent manner.[17] Continuous TDF/FTC is recommended in the populations of female transgender, men that have sexual intercourse with other men, and individuals chronically infected with hepatitis B virus.[17] For intermittent or TDF/FTC, 2 pills should be taken 2 to 24 hours before the first sexual intercourse followed by 1 pill each 24 hours during the time course of sexual activity and until 48 hours after the last sexual encounter.[4,17,18] Episodic or on-demand PrEP has not been shown to be effective for vaginal exposure. Monotherapy with TDF should be considered in case of FTC intolerance.[16] Clinical referral can be performed by physicians or other health care professionals and community-based organization workers. Additionally, the individual can schedule a specialized consultation in a hospital with the Infectiology specialty.

The prevalence of **sexually transmitted infections (STIs)** is positively linked to a higher incidence of HIV-infection, as they are usually indicators of unprotected intercourses.[9,19] The risk of contracting STIs increases with the increase in the number of sexual partners and is higher if the use of condoms is inconsistent or incorrect.[20,21] Moreover, lack of vaccination can also contribute for the higher risk of contracting an STI.[20] HIV-infected individuals should be screened for STIs at the time of diagnosis and annually afterwards (or when compatible symptoms appear).[21] In order to diagnose STIs it is crucial to collect the epidemiological and sexual history of the individual, perform a clinical examination (look for signs of severe infection and of proctitis) and perform diagnostic investigations such as stool cultures, antimicrobial susceptibility testing of relevant pathogens, nucleic acid amplification testing and serological tests, since treatment depends on the disease-causative agent.[19-21] However, available vaccination against some of the microorganisms responsible for these diseases (e.g., HBV, HCV and HPV), safe-sex practices, PrEP (for those at risk of contracting HIV) and treatment of at risk partners can prevent STIs.[20] If the patient suffers from recurrent reinfections and/or feels the treatment is failing, clinical referral is recommended. Nonetheless, this referral should not delay the treatment of both the patient and the respective partner.

Vaccination of adult individuals living with HIV

Vaccination of individuals living with HIV was a cause of concern due to the possibility that vaccination could cause activation of the immune system and promote the replication of HIV.[22] Consequently, the levels of viral RNA would increase and accelerate the progression of the disease.[22] However, it has been shown that the increase in viral load was rare and, if present, was transient and clinically irrelevant in patients under combined ART.[10] Thus, it is recommended that this population follows an immunization schedule.[10,23] Vaccination is especially important for these individuals due to the higher risk of infectious diseases and to the hypothesis that they might experience more severe forms of the diseases.[10] Moreover, individuals living with HIV might have an increased risk of contracting some infections such as sexually transmitted diseases (e.g., hepatitis A, hepatitis B and HPV).[10] Generally, vaccination is safe if the $CD4^+$ T cells count is not lower than 200/µL and, thus, the individuals have a preserved or reconstituted immunity.[23,24] When the $CD4^+$ T cells count is lower than 200/µL, vaccines with attenuated organisms (e.g., measles, rubella and yellow ever vaccine) are not recommended.[23,25] In these cases, ideally, the vaccines should be administered after six months of a confirmed $CD4^+$ T cells count higher than 200/µL. In the case of individuals with mild immunodeficiency ($CD4^+$ T cells count between 200-350/µL), the recommendation should be discussed on a case-by-case basis to consider the risk of acquiring the infection naturally *versus* the probability of developing the infection as a side effect of the vaccine.[24,26] Also, some guidelines refer that two attenuated vaccines should not be administered simultaneously as there are doubts about the safety, efficacy and immunogenicity of this procedure.[24] Additionally, as it is recommended for the general population, attenuated vaccines should not be administered if the individuals were treated with blood-derived products, such as immunoglobulins.[27] A summary of the inactive (Table I), attenuated

(Table II) and travel-related (Table III) vaccines recommended for HIV patients and the respective recommendations for their administration are listed below.[24,28]

Preconception, pregnancy and childbirth

Vertical transmission of HIV was drastically decreased with the introduction of ART.[7] Nowadays, natural conception is the best option for conceiving if the infected partners are under ART, if there is good treatment adherence and if HIV RNA has been undetectable for more than 6 months.[29] Therefore, and to ensure the lowest possible risk of vertical transmission, a general clinical and laboratory evaluation should be performed before conceiving. Moreover, addictions such as alcohol, drugs and tobacco should be treated.[30] If vaccines included in the national immunization plan are missing, they should be administered, and folic acid supplementation should be initiated.[29,30] Additionally, a screen for STIs, a cervical cytology and HPV genotyping should be conducted.[29,31] Finally, prompt ART initiation or optimization is warranted if the individuals are not virologically suppressed.[29] In serodiscordant couples, if the infected partner has detectable HIV RNA, and/or adherence to ART is not guaranteed, PrEP is advised.[30] Semen washing may be considered if viral suppression is not achieved despite adherence to optimized ART.[31] Referral to a fertility

TABLE I – LIST OF INACTIVE VACCINES RECOMMENDED FOR INDIVIDUALS WITH HIV. THE VACCINES ARE ORGANIZED IN ALPHABETICAL ORDER OF THE DISEASE TO BE PREVENTED

Disease	Vaccine type	Administration	Recommendation	Remarks
Diphtheria and Tetanus	Toxoid	>10 years old. 1 dose at 25, 45 and 65 years old. Every 10 years afterwards	Universal	DGS
Flu (influenza virus)	Inactivated	1 annual dose	Universal	
Haemophilus influenzae type B	Conjugated	1 dose (if not given during childhood)	Sickle cell anemia, leukemia and functional or anatomical asplenia	
Hepatitis A	Inactivated	2 doses with a 6 to 12 months interval	Non-immune	BHIVA recommends 3 doses if $CD4^+$ T<350/µL
Hepatitis B	Subunit	3 doses: 0, 1 e 6 months	Non-immune	
Human papilloma virus	Virus-like particle	3 doses	< 26 years old	
Meningitis (Tetravalent for serogroups ACYW135)	Conjugated	1 dose; reinforcement after 5 years	To be considered in adults that were not vaccinated	BHIVA recommends 2 doses with a 2-month interval; reinforcement if the risk is maintained after 5 years
Meningitis B	Conjugated + outer membrane vesicles	2 doses	<25 years or in the presence of risk factors	
Pneumococcal disease	Conjugated, 13 valent	1 dose	If not taken previously	
Pneumococcal disease	Polysaccharide, 23 valent	1 dose after conjugated vaccine; repeat 5 years later and at 65 years old (if the last dose was > 5 years before)		DGS, ACIP, BHIVA
Poliomyelitis (poliovirus types 1, 2 and 3)	Inactivated	3 doses at 0, 1-2 and 6-12 months. 1 reinforcement 6 to 12 months after	Incomplete immunization scheme. If travelling to a risk country: 1 dose if > 10 years after finishing the immunization scheme	DGS

Sources: Geretti et al, 2016; *Programa Nacional de Vacinação*, 2020. ACIP: advisory committee on immunization practices; BHIVA: British HIV Association; DGS: *Direção-Geral da Saúde*.

TABLE II – LIST OF ATTENUATED VACCINES RECOMMENDED FOR INDIVIDUALS WITH HIV				
Disease	**Administration**	**Recommendation**	**Contraindications**	**Remarks**
Measles, mumps and rubella (VASPR)	1 dose (DGS) 2 doses with 4 weeks interval (ACIP)	Nonimmune individuals and $CD4^+$ T >200/µL for ≥6 months	$CD4^+$ T < 200/µL	
Varicella	2 doses with 4 weeks interval ACIP: 2 doses with 3 months interval	Nonimmune individuals and $CD4^+$ T >200/µL for ≥6 months	$CD4^+$ T< 200/µL	For nonimmune individuals without history of disease and antibodies; avoid salicylates in the following 6 weeks
Shingles	1 dose Some studies recommend 2 doses (safe and immunogenic)	Age >60 years and $CD4^+$ T >200/µL for ≥6 months	$CD4^+$ T <200/µL	Recommended by BHIVA; Without recommendation by ACIP Do not administrate this vaccine to individuals that took the vaccine for varicella (ACIP)
Yellow fever	1 dose	Risk zone	$CD4^+$ T < 200/µL Age > 60 years (BHIVA) Any age and asymptomatic with $CD4^+$T: 200-499 cells/mm^3 (ACIP)	Consider revaccinate in >10 years if risk remains (ACIP)

Sources: Geretti et al, 2016; *Programa Nacional de Vacinação*, 2020; Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents. ACIP: advisory committee on immunization practices; BHIVA: British HIV Association; DGS: *Direção-Geral da Saúde*.

unit is advised when the female living with HIV (who usually has a lower ovarian reserve), is 35 years old or older and has been trying to conceive for more than 6 months without success.[30,31]

If there is good ART adherence, the risk of transmission of HIV infection during pregnancy is lower than 1%.[32] However, some additional care should be taken during pregnancy and delivery of females living with HIV. C-section is recommended for females that are not under ART, have an unknown viral load or have HIV RNA values higher than 1000 cp/mL.[30] Screening for HIV, HBV, HCV and for syphilis should be performed in the first and third trimesters of pregnancy.[29] If there was no HIV screen test on the third trimester, a fast HIV test should be performed at delivery.[30] Moreover, the partner should be screened as well.[30] An undetectable viral load should be ensured in the cases where there is recommendation for invasive prenatal diagnostic techniques.[30] If needed, treatment of other STIs and adjustments to ART should be prescribed.[29] Clinical referral to an Obstetrics consultation should be performed early in the pregnancy. After childbirth, breastfeeding in HIV infected women, even under suppressive ART, is currently not recommended.[29] Nevertheless, studies are being conducted on this topic and recommendations might be updated.

/ Conclusions

Undetectable viral loads achieved with ART regimens, coupled with concurrent STI treatment are determinant factors to successfully prevent HIV transmission. A preserved or reconstituted immunity is a decisive factor for vaccination, which is critical to prevent the acquisition of infectious comorbidities. The implementation of treatment strategies tailored for the population living with HIV and of PrEP for people at risk of contracting HIV ameliorates the quality of life of these populations and allows for a better control of the HIV pandemic.

/ Conflicts of interest

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TABLE III – LIST OF TRAVEL-RELATED VACCINES RECOMMENDED FOR INDIVIDUALS WITH HIV				
Disease	**Vaccine type**	**Administration**	**Contraindications**	**Remarks**
Hepatitis A	Inactivated	2 doses with 6 to 12 months of interval		BHIVA recommends 3 doses if $CD4^+$ T<350/µL
Cholera	Inactivated + subunit	3 doses in alternate days; oral administration		
Japanese Encephalitis	Inactivated (from Vero cells)	2 doses with 4 weeks interval, 1 reinforcement after 1 year		
Tick fever	Inactivated	3 doses at 0, 1-3 and 5-12 months		
Rabies (pre- exposure) Inactivated (from cell culture) 3 doses at days 0, 7 and 28 Serological test 2 to 4 weeks after taking the vaccine – if <0.5 UI/mL perform a vaccine reinforcement (possibly double dose) followed by a serological test. If the disease risk persists, repeat serological test after 1 year and then every 3 to 5 years (BHIVA).				
Typhoid fever, IM (Capsular polysaccharide vaccine)	Inactivated	1 dose		Reinforcement every 3 years if the risk of disease is maintained
Typhoid fever, oral (Ty21a)	Attenuated	2 doses with 1 week interval	CD4+ T<200/µL Contraindicated for all (BHIVA)	
Yellow fever	Attenuated	1 dose (for life)	$CD4^+$ T< 200/µL Age: >60 years (BHIVA) Any age and asymptomatic with $CD4^+$ T: 200-499 cells/mm^3 (ACIP)	Consider revaccinate in >10 years if risk remains (ACIP)
Meningitis (ACYW135)	Conjugated	1 dose		BHIVA recommends 2 doses with 2 months interval; reinforcement after 5 years if the risk is maintained
Poliomyelitis (poliovirus types 1, 2 and 3)	Inativated	3 doses at 0, 1-2 and 6-12 months; reinforcement		Travel to country of risk: 1 dose if >10 years after completing immunization scheme; for life (DGS)

Sources: Geretti et al, 2016; *Programa Nacional de Vacinação*, 2020; Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents. BHIVA: British HIV Association; IM: intramuscular; DGS: *Direção-Geral da Saúde.*

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