ASSOCIATION OF
RINGSIDE PHYSICIANS

Blood-borne Infection Prevention in Combat Sports

Position Statement of the Association of Ringside Physicians

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POSITION STATEMENT (ABSTRACT)

The Association of Ringside Physicians (ARP) emphasizes the importance of screening combat sports athletes for blood-borne infections, including hepatitis B, HIV, and Hepatitis C, to mitigate transmission risks and ensure participant safety. Although transmission of hepatitis B and C and HIV in combat sports are rare, protecting athletes is of utmost importance. It is the recommendation of the ARP that all fighters participating in combat sports in which the presence of blood is a common occurrence and is allowed during competition, should undergo testing for HIV, Hepatitis B (HBV), and Hepatitis C (HCV). Testing should be conducted using serum samples, as rapid tests are not considered acceptable for accurate results. Testing for HBV, HCV and HIV should optimally be done within 3 months of competition, but within 6 months is acceptable. Athletes whose tests suggest active HBV, HCV or HIV infection should be disqualified from competition in sports where blood is common and allowed. Athletes with cured prior HCV infection may be cleared for competition in all combat sports. Athletes with prior HBV infection and no detectable HBV DNA in blood can be cleared for competition in all combat sports. Athletes with latent HBV infection with detectable HVB DNA in blood have a small risk of disease reactivation, so they should not be cleared. Athletes with

HIV infection should be disqualified indefinitely regardless of current viral load or past/present antiretroviral therapy.

PREAMBLE: DEVELOPMENT OF THIS STATEMENT

The Association of Ringside Physicians (ARP) is an international, non-profit organization dedicated to the health and safety of combat sports athletes. This Position Statement represents a collaborative effort among the ARP board of directors, emeritus board, and subject matter experts from the membership. It seeks to highlight issues in blood-borne infections unique to combat sports athletes.

The screening measures for blood-borne infections in combat sports athletes are critical to ensure the safety and health of all athletes. Blood-borne infections, such as HIV, HBV, and HCV, can be transmitted through contact with infected blood. Although there exists a small risk transmission during combat sports, minimizing this risk is of utmost importance to protect athletes.

An extensive literature search including but not restricted to Pubmed, Cochrane Reviews and non-indexed peer-reviewed articles published in online medical journals was performed to determine relevance of articles to the above blood-borne infections, combat sports, or sports in general. After review, discussion, and revision, the manuscript was formally approved by the authors and the entire board of directors as the official Position Statement of the ARP.

Hepatitis B

Epidemiology

There are an estimated 296 million carriers of HBV worldwide, with 1-5 million new infections per year, a prevalence of 3.5% and an estimated 820,000 annual mortality [1,2]. Since HBV is resistant to a spectrum of temperatures, as well as resistant to drying and alcohol, it can remain on surfaces for up to a week and has an increased risk of transmission when compared to HIV and HCV [3]. Moreover, when compared to HIV, HBV infection causes a higher viral load which can lead to an increased risk of transmission [3].

Transmission of HBV occurs through vertical transmission in pregnancy, sexual intercourse, mucus membrane exposure to infected blood or other body fluids, or percutaneously via contaminated needles [3,4]. Since HBV has a high risk of transmission, it is estimated that in sports, the risk of contracting HBV is one in every 850,000 to 4.25 million games [5]. It should be noted that this risk was estimated on extrapolating data from the national football league. There have been case reports of transmission of HBV in sports, however they are isolated cases and pertain to sumo wrestling, soccer and cross country sports [6,7,8]. There have been no reported cases of HBV transmission in sanctioned combat sports [3,5].

Pathophysiology

HBV is a partially double-stranded DNA virus belonging to the Hepadnaviridae family [9]. HBV is resistant to a wide range of temperatures and can even stay active on surfaces at 44^{o}C for 7 days [10]. Within the double-

stranded DNA genome of HBV are 4 genes; the S, C, X and P genes which correspond to the surface envelope, core antigens, transcription proteins and polymerase proteins respectively. [11,13].

After reaching the host bloodstream HBV initially attaches to hepatocytes, the primary target cells in the liver, through interactions between its surface antigen (HBsAg) and host cell receptor [13,14]. After attachment, the virus enters the hepatocytes and undergoes DNA integration followed by viral protein transcription via covalently closed circular DNA (cccDNA) [15-18]. The cccDNA serves as a template for transcription of viral RNA, ensuring persistent infection and viral replication [15,17,18].

The host RNA polymerase transcribes viral messenger RNA to eventually encode viral proteins such as nucleocapsids which contain viral DNA. Once this occurs, HBV is released via exocytosis into the blood for further infection of other hepatocytes.

HBV induces both the innate and adaptive immune response. HBV elicits cellular lysis by CD4+ and CD8+ lymphocytes due to immune system recognition of HBsAg on infected cells [11]. Cytotoxic T lymphocytes (CTL), which are a part of the adaptive immune response, clears an HBV infection by killing infected cells and by producing antiviral cytokines such as IL-4, IL-13 and TNF-α [19,20]. During this process however, CTLs and inflammation from the cytokines induce hepatocellular damage.

During this acute phase, which lasts 1-6 months, the majority of patients are asymptomatic, but they can present with anorexia, nausea, vomiting, myalgia and icterus [13,21]. In both the acute and chronic phase, prolonged inflammation can lead to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [12,13]. Hepatitis D can also occur during a HBV infection as hepatitis D uses HBV surface antigen to infect hepatocytes [22]. Once the infection is eradicated, the prognosis is good for patients as less than 5 percent of adults progress from acute to chronic hepatitis B [23]. A chronic HBV infection is defined as persistence of HBsAg for more than six months and consists of 4 phases [13].

In the immune tolerant phase, there are high levels of HBV replication, as well as elevated HBeAg and HBV DNA. Majority of patients are asymptomatic during this phase due to immune tolerance and there is no active liver disease [16]. Immune-active is the next phase, which is characterized by HBeAg seroconversion and an increase in HBeAg clearance [25]. Inactive chronic HBV is the next phase. During this phase, patients are HBeAg negative and anti-HBe positive with undetectable HBV DNA [13,24]. During the last phase, immune-active with HBeAg negative, HBV replication increases which leads to active liver disease [26]. A chronic HBV infection can lead to cirrhosis, liver failure, or HCC. Additionally, HBV infection can be complicated by immune-mediated extrahepatic manifestations, such as polyarteritis nodosa, membranous nephropathy and membranoproliferative glomerulonephritis [27,28].

Diagnosis:

The diagnosis of HBV infection requires considering the probable stage of infection in the patient as well as differentiating immunity status. There are 3 main components of blood tests for HBV: surface antigen (HBsAg),

antibody against core antigen (Anti-HBc), and antibodies against surface antigen (Anti-HBs) [29,30]. The key finding that establishes a current HBV infection is positive HBsAg [31]. Testing positive for HBsAg or anti-HBc IgM is indicative of an acute infection. A positive result for over 6 months establishes a chronic infection [32]. During the chronic phase, both HBsAg and Anti-HBc IgG will be positive. Further testing is done to detect replication, transmissibility and viral load. HBeAg is a marker of HBV replication and transmissibility while HBV DNA quantifies viral load [29,31]; these are not required tests for combat sports athlete screening. An undetectable HBeAg with development of anti-HBe indicates that the patient has immunity or is an inactive carrier.

For the purposes of combat sports, the diagnosis of active HBV infection is made by a positive hepatitis B surface antigen, and this would preclude participation in combat sports in which blood is common and accepted due to active infectious status. A negative HBsAg essentially rules out active HBV infection [4-6,31].

	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	HBV DNA	Cleared for Competition
Immunity from vaccination	undetectable	+	undetectable	undetectable	undetectable	Not tested	Yes
Immunity from resolved infection	Undetectable	+	IgG+	Undetectable	Undetectable	Undetectable	Yes
Acute infection	+	Undetectable	IgM+	+	Undetectable	Undetectable	No
Chronic infection [Active]	+	Undetectable or +	IgG+	+	Undetectable	>2000 IU/mL	No
Chronic infection [Inactive]	+	Undetectable or +	IgG+	Undetectable	+	<2000 IU/mL	No

Table 1: Interpretation of Hepatitis B serology

Treatment

Acute HBV infection is self-limiting in more than 95% of immunocompetent adults and requires no treatment [31]. Therefore, patients that require pharmacological treatment are those with chronic or severe disease, with a focus on quality of life and improving survival. Currently the treatment goal is to achieve sustained suppression of HBV replication and liver inflammation, with the goal of preventing complications such as cirrhosis or HCC. Treatment has been documented to reverse liver fibrosis as well as reduce the risk of HCC [32]. Treatment

strategy includes nucleos(t)ide analog medications and/or pegylated interferon. The FDA approved medications for treatment include two formulations of interferon alpha (conventional and pegylated) and five nucleos(t)ide analogues (Lamivudine, Adefovir, Entecavir, Telbivudine, and Tenofovir) [32].

Prevention

In the United States, an estimated 580,000 to 2.4 million are living with HBV infection, with nearly 66% of patients not aware that they have contracted the infection [29]. Since infection is transmitted through contact with infected blood or body fluids, avoiding high risk activity such as multiple unprotected sexual encounters or sharing needles is imperative.

Prevention of HBV infection for the individual is done by avoiding transmission and inducing immunity through immunization. Due to the persistent transmission of HBV in the United States, the Centers for Disease Control and Prevention (CDC) published new recommendations for general screening in 2023 [29]. The rationale was to start with a universal screening test for adults older than 18 years old with a triple panel that includes surface antigen, surface antibody and core antibody results. This contrasts with previous recommendations that recommended only testing patients who were deemed high risk for infection. Including universal screening for all adults reduces ongoing transmission and is considered cost efficient to help prevent infection progression to cirrhosis, HCC and death. This also helps identify patients who no longer have detectable immunity to hepatitis B and may benefit from booster vaccination.

Recommendations for combat sports athletes to prevent infection are identical to other persons, including avoiding IV drug use, avoiding unprotected sexual encounters, and adhering to screening recommendations from the CDC. If the athlete does not have immunity, it is recommended for the athlete to obtain updated HBV vaccination. Activities in which the risk of exposure to blood is substantial should be prohibited for athletes with acute or chronic infection. It is this panel's expert opinion that testing for HBV should be done within 3 months of competition.

PROCEDURES FOR ATHLETES TESTING FOR HEPATITIS B

The various amounts of serological testing of HBV may make it difficult to interpret whether the combat athlete is safe to compete. The combat athlete should get tested with HBsAg, Anti-HBs, and Anti-HBc. The first step in determining if an athlete can compete is to determine the status of infection. An acutely infectious athlete will test positive for HBsAg and should not be cleared to compete. Athletes with negative HBsAg, Anti-HBc and Anti-HBs may compete, but are considered not immune and recommended to get updated immunization. Athletes with negative HBsAg, Anti-HBc and positive Anti-HBs are cleared to compete and are considered immune.

An athlete who has a history of a prior HBV infection will have different serologic test results. A typical example is an athlete that tests negative for HBsAg, but positive Anti-HBc and Anti-HBs. In this case, HBV DNA should be tested to detect viral material that can be transmitted through blood. Only those with undetectable HBV

DNA should be cleared to compete. These tests should be done within 3 months of each fight, and the decision to clear before each fight will rely on the HBV DNA being undetectable.

HIV

Epidemiology

Human Immunodeficiency Virus (HIV), which causes Acquired Immunodeficiency Syndrome (AIDS), was first identified in 1981. Since its discovery, it is estimated to have caused over 50 million fatalities globally [33]. In 2022 an estimated 39 million people were living with HIV, with an annual incidence of 1-3 million cases [34,35]. Of all cases globally, Sub-Saharan Africa accounts for more than 50% of cases [34]. Although the incidence of new cases has declined in twenty years, AIDS remains one of the top ten causes of death globally [36].

Transmission of HIV is primarily through sexual intercourse, sharing contaminated needles and via vertical transmission during pregnancy, childbirth and breastfeeding [37]. Although there is a risk of transmission of HIV in sports, with an increased risk with contact and collision sports, the risk of transmission is exceedingly low [38]. Transmission can occur from bleeding wounds or abrasions from an infected athlete to exposed mucus membranes of another athlete. The increased risk from contact sports is due to the higher risk of bleeding injuries and prolonged close contact [5].

It is estimated that the risk of contracting HIV in any sport is less than one in a million games [33, 5]. In regard to HIV, there have been no documented confirmed reports of HIV transmission during any sport, although it is still estimated that professional boxing and professional mixed martial arts carries the highest risk of transmission of HIV [5]. There have been no reported cases of HIV transmission in any sanctioned combat sports but there have been few case reports of HIV transmission during altercations [39-42].

Pathophysiology

HIV is a retrovirus that belongs to the family of Retroviridae, that primarily infects monocytes and macrophages [43,44]. Two types of HIV are known, HIV-1 and HIV-2, with the former having higher infectivity and virulence [45]. The HIV virus is composed of two copies of positive-sense single stranded RNA. Being a retrovirus, HIV integrates its own RNA into host cellular DNA via reverse transcriptase [44]. This process is error-prone, leading to genetic variability and the generation of diverse viral variants [46]. Upon activation, host RNA polymerase transcribes the viral DNA into messenger RNA (mRNA), which is then translated into viral proteins. The RNA genome of HIV includes structural proteins, regulatory proteins, its own reverse transcriptase, nucleocapsid proteins, proteases and several copies of p24, the capsid protein for HIV [44,47]. Once transcribed by the cellular host, HIV-RNA is packaged into p24 and eventually forms a mature, infectious virion [48]. Once the virus is released, it spreads throughout the body in the bloodstream and extracellular fluid until it encounters a CD4+ T cell or dendritic cell. The HIV virus then attaches to the host cell through interactions between its envelope glycoprotein (gp120) and CD4 as well as CXCR4 receptor molecules present on the surface of CD4+ T cells, as well as co-receptors such as CCR5 on dendritic cells [49,50]. Once attached, the HIV virus fuses with the host cell and the viral contents are released within the cell. The virus then continues replication.

The infected CD4+ cells then remain within lymph nodes for 2 - 4 weeks until HIV rapidly multiplies within the body due a poor host response to the virus. This marks the beginning of the acute phase of an HIV infection. During this phase, it is common for the patient to experience fever, fatigue, myalgia, rash and painful lymph nodes [47,51,52]. In this phase, CD4+ T cell numbers decrease due to cellular lysis and activation of CD8+ T cells which help kill infected CD4+ cells [53]. Plasma RNA levels decline due to the immune response, which takes weeks to months and marks the beginning of the latent phase [54]. In the latent phase, anti-HIV antibodies become detectable, indicating seroconversion and CD4+ count increases but will not go back to normal [55]. Over a period of months to years, the CD4+ cell count declines, effectively decreasing host immune response and HIV-RNA replication continues until the CD4+ count drops below 500 cells/microL Between 500 cells/microL and 200 cells/mircoL, patients are prone to infections with oral candidiasis, herpes simplex or varicella zoster [56]. As the CD4+ count falls below 200 cells/microL; patients become highly susceptible to infections from Mycobacterium avium, Mycobacterium tuberculosis, Pneumocystis carinii, cytomegalovirus (CMV) and toxoplasmosis [55,56]. These infections, along with other conditions such as Kapsoi sarcoma and wasting syndrome, constitute AIDS-defining conditions. In order to be diagnosed with AIDS, a patient must have a CD4+ count less than 200 cells/microL or have an AIDS-defining condition [57,58]. The median survival time of patients with a CD4+ count of less than 50 cells/mircoL is 12 -18 months [59].

The initial symptoms of HIV are nonspecific and occur 2 - 4 weeks after exposure [5,34,35]. The most common are fever, lymphadenopathy, myalgia/arthralgia, sore throat, GI symptoms and rash but none of them are specific to HIV [37,38]. The constellation of symptoms is known as acute retroviral syndrome and occur during the initial HIV infection [44,45]. During the latent stage, patients are usually asymptomatic. Before a patient's CD4 count decreases below 200 cells/microL, they will have nonspecific symptoms such as fatigue, night sweats, weight loss, fever and generalized lymphadenopathy [49,53]. More importantly, infections such as oral candidiasis, bacterial folliculitis, herpes simplex and varicella zoster may manifest [54,56,57]. Once the patient has less than 200 cells/microL or develops an AIDS-defining condition, the patient then has AIDS. At less than 200 cells/microL, the patient is at risk for Pneumocystic jirovecii, HSV, Progressive multifocal leukocenephalopathy and cryptosporidium [56-58]. At less than 100 cells/microL, there is a risk of developing cerebral toxoplasmosis, cryptococal meningitis and disseminated CMV infections [49,53,56]. At less than 50 cells/microL, there is a risk of developing Mycobacterium avium complex [56-58].

Diagnosis

The diagnosis of HIV involves testing for both the antigen and antibody for HIV 1 and 2 via an immunoassay [60.62]. These tests are done as initial screening tests and can be done as either a combination of HIV antigen/antibody test (4th generation) or a HIV antibody ELISA [63-65]. The combination of the antigen/antibody test incorporates both HIV-1, HIV-2 and the p24 antigen. These will be positive 3 weeks to 3 months after first exposure. If positive, a confirmatory test is done via a HIV 1 and 2 antibody differentiation immunoassay [60,62]. If this test is positive, it confirms the diagnosis of HIV [64,64]. Newer 5th generation tests are able to distinguish an

infection with HIV-1 and HIV-2 [65,66]. If the test is negative or indeterminate, a nucleic acid amplification test [NAAT] is done which will determine the presence of HIV-RNA [60]. The benefit of a NAAT is that it can detect HIV earlier than any other test and can be done 10 days after suspected transmission [61]. It should be noted that patients that have a known exposure or potentially exposed should have a repeat antibody/antigen test done 4-6 weeks after exposure, and if negative then, repeated again 3 months after exposure [67,68].

There are no high-quality studies that give recommendations regarding the frequency of HIV testing for athletes in combat sports, and each state has varying recommendations on frequency of testing. Given that there exists a risk of transmission, it is recommended that an athlete be tested every 3 to 6 months, with a strong preference for every 3 months. In athletes that are high risk, we recommend that athletes be tested every three months. If the athlete has a known exposure to HIV, they should be disqualified from competition in sports where blood is common and accepted until they test negative for HIV at least 3 months after the exposure.

Treatment

The goal of HIV treatment is to disrupt the process of the virus multiplying and reduce the amount of virus in the body by targeting different stages of its life cycle [69-71]. Although HIV cannot be cured, the use of antiretroviral therapy [ART] can reduce transmission, reduce viral load, increase the CD4 count and improve the patient's quality of life [72-75].

There are six drug classes that encompass ART. Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Integrase Strand Transfer Inhibitors (INI) , Fusion Inhibitors [FI] and Chemokine receptor antagonists[76-80]. Regardless of a patient's stage of HIV, all patients require treatment with ART. Although several ARTs exist, generally the treatment regime consists of 2NRTIs plus a NNRTI or 2NRTIs plus 1 PI or 2NRTIs plus INSTI or 1 NRTI plus 1 INI [Dolutegravir and lamivudine specifically] [81-86]. The selection of a treatment regime is dependent on drug toxicity, underlying illnesses, drug interactions, HIV resistance testing and access to care [84-86].

PROCEDURE FOR ATHLETES WHO TEST POSITIVE FOR HIV

Athletes with HIV infection (past positive HIV antigen/antibody test (4th generation) or HIV antibody ELISA, regardless of current viral load or past ART treatment) should be suspended indefinitely from competition in sports where blood is common and accepted, given the increased risk for viral transmission.

Hepatitis C

Epidemiology

There are an estimated 58 million chronic carriers of HCV, with 1-5 million new infections yearly and a prevalence of 0.7 percent [87,88]. It should be noted that these numbers are estimates due to lack of surveillance globally.

Transmission of HCV is primarily through use of contaminated needles. Other less common modes of transmission are through blood transfusions, sexual intercourse, body piercing and vertical transmission in pregnancy [89,90]. There have been no cases of HCV transmission through sports [91,92].

While no case reports or studies have linked sanctioned combat sports with HCV transmission, there are several case reports of persons without other risk factors or exposures acquiring HCV from bloody fights. These include a sheriff who had blood splashed into his eyes while breaking up a fight between two incarcerated individuals [93], a policeman whose hand was lacerated from punching a man in the mouth while making an arrest [94], and two family members who had a bloody fight and afterwards shared a handkerchief to wipe the blood off their bodies [95]. Given these documented cases, plus the significant proportion of HCV cases with no known exposure and one study showing contact sports to be a risk factor [96], it would appear there is an increased risk of HCV transmission between persons engaging in combative activities in which blood or body fluids are possibly exchanged.

Pathophysiology

HCV is a single-stranded positive-sense RNA virus belonging to the Flaviviridae family [97]. The genome of hepatitis C encodes three structural proteins, a core protein, two envelope proteins [E1 and E2], p7 and NS2 which are essential for viral production, and five nonstructural proteins that are required for replication [98-100]

HCV initially attaches to host cells, primarily hepatocytes in the liver, via mediation of glycosaminoglycans, CD81, claudin-1 and receptor B1 [101]. After attachment to the host cell, endocytosis occurs and the HCV positive-stranded RNA is uncoated which is then translated into a single polyprotein precursor.The polyprotein is then cleaved by both host and viral proteases into individual viral proteins and structural proteins [97,101]. These proteins are then transported to the host cell endoplasmic reticulum and form a replication complex with RNA dependent RNA polymerase [97,102,103]. The replication complex contains both a negative-sense and positive sense RNA [102,103]. Once viral genome replication occurs, it is packaged into the core and envelope proteins and it is released from the host cell. HCV continues to infect hepatocytes, which lasts 2 to 6 weeks until symptoms appear; however most patients are asymptomatic as symptoms occur in only 20% of patients [104].

Symptoms of HCV infection are nonspecific and include myalgia, fever, nausea and vomiting. Jaundice occurs only in 20% of patients [101]. For patients with an acute HCV infection, 50.8% of cases progress to chronic HCV infection [105]. A chronic infection is defined as persistent HCV-RNA for greater than 6 months [101,106]. Progression from an acute to a chronic infection is thought to be from an altered CD4+ T helper cell and cytotoxic T

cell response which causes necroinflammatory lesions in hepatocytes, however HCV is not cytopathic to cells. HCV employs various mechanisms to evade the host immune response, including rapid mutation rates, interference with innate immune signaling pathways, and modulation of host cell apoptosis [101].

Chronic inflammation then triggers fibrosis and eventually cirrhosis. The rate of fibrosis is increased in those with comorbid hepatitis B, HIV, alcohol use disorder and male sex [107]. Liver cirrhosis can then lead to ascites, spontaneous bacterial peritonitis, bleeding from esophageal varices, jaundice, and hepatic encephalopathy [97,103,104]. Extrahepatic complications of hepatitis C include insulin resistance, cardiomyopathy, membranoproliferative glomerulonephritis, porphyria cutanea tarda, mixed cryoglobulinemia and lichen planus [104,109-111]. Most importantly, approximately 50% of patients with chronic hepatitis C develop hepatocellular carcinoma, which carries a high mortality rate [112].

Diagnosis

Routine screening of HCV is recommended for all persons 18 years and older, according to recommendations from the CDC [113,114]. Justification for this approach includes HCV being a major source of morbidity and mortality, the high prevalence of asymptomatic infection, lack of a vaccine, and striving for lower transmission rates. In the general population, screening is recommended at least once in a lifetime, and periodically in persons with persistent risk factors [113]. These include IV drug use, prior blood transfusion from non-screened persons, sex with persons of known infection status, tattooing and body piercing, and incarceration [114-122]. Twenty to forty percent of patients infected with HCV do not have any risk factors and as a result, have acquired them by unknown means [115,123-127].

Screening for HCV infection involves a blood sample analyzed for the anti-HCV antibody using an immunoassay approved by the US Food and Drug Administration. Most samples require venous blood from phlebotomy, but point-of-care tests using capillary blood from fingerstick are also accurate [122,123]. A positive antibody test suggests either active HCV infection, past HCV infection, or rarely a false-positive with no past infection [113-115]. When anti-HCV is positive, a test for HCV-RNA should then be done, optimally with a “reflex” testing method where the same blood sample is automatically and immediately followed up with a HCV-RNA test [113,114]. An FDA-approved test with a detection level of <= 25 IU/ml should be used [114]. If the RNA test is positive, this confirms active infection [114]. If RNA is negative, then the patient is considered to have a cured past infection [115]. Since there is a delay of up to 3 months between time of infection and time of antibody seropositivity [126], initially negative results in persons with exposure or risk factors may need to be repeated in 3 months [127-129].

There are no studies to guide recommendations for timing and frequency of testing for HCV in combat sports athletes and each state varies in their recommendations [129]. In the presence of other risk factors for infection, however, infection can occur subsequent to a negative test, so repeated testing may be necessary to detect infection. Testing within 3 months of competition is recommended to detect recently acquired infections. Though

risk-based testing could reduce the testing burden, assessment of athletes' high-risk behaviors would be unreliable and inaccurate due to self-underreporting. Therefore, a more standardized screening interval is advised.

Treatment

Modern multi-drug direct action antiviral (DAA) therapy such as with ledipasiv/sofosbuvir, achieves cure in over 95% of persons with only 8 to 12 weeks of therapy [127]. DAA is safe and easy to administer. Retreatment may be needed in some high-risk persons such as those with cirrhosis or infection with genotype 3 virus [127]. Those with undetectable HCV-RNA 12 weeks after treatment are considered to have achieved sustained virologic response (SVR) and are considered cured, with the same follow-up and testing requirements as if they were never infected [127]. However, while anti-HCV antibodies usually persist lifelong, they do not protect from reinfection. Therefore, further testing should be based on risk factors for infection [114].

PROCEDURES FOR ATHLETES WHO TEST POSITIVE FOR HCV

Athletes with positive anti-HCV and HCV-RNA have active infection and may transmit the virus through blood or other body fluids, so they should be disqualified from competition in sports where blood is common and accepted. Athletes with positive anti-HCV but undetectable HCV-RNA are considered immune and have achieved SVR and may be cleared for all combat sports [129]. Future testing of these athletes should continue to include both anti-HCV and HCV-RNA.

Discussion

Testing for HIV, HBV and HCV is crucial for ensuring the safety of athletes in combat sports due to the higher risk of blood-to-blood contact. The authors, however, acknowledge the limited amounts of case reports describing transmission of these viruses in combat sports and the potential these sports carry for transmission. The statements formulated are based on data extrapolated from the literature, collective expertise, and review of current practices from each state commission and practicality.

Testing for HIV, HBV and HCV should be done for all combat sports athletes participating in any activity in which blood exposure is common and accepted due to the increased risk of transmission of these blood borne infections. Testing must be done via serum samples. Rapid tests are not acceptable means of testing.

The rationale for the 3 to 6 month testing window prior to competition is based on several factors. HIV, HBV and HCV can cause serious morbidity and increase the risk of mortality and can be lifelong infections, so prevention is paramount. Each virus also has a period of non-detectability between exposure and evidence of infection, sometimes up to 3 months. This time frame gives athletes and regulators a reasonable opportunity to secure the testing, submit documents, and act on results. Though testing within 3 to 6 months of competition imposes a significant burden upon athletes and regulators, it is necessary to preserve the integrity of combat sports while

protecting athletes from serious infections. Theoretically, a reduced frequency of testing for athletes without risk factors or known exposures would reduce the testing burden, but implementation of risk-factor-based screening is difficult or impossible. Therefore, the more frequent testing interval is recommended.

Athletes should optimally be tested for HIV, HBV and HCV within 3 months of competition, however within 6 months is acceptable. Testing within 3 to 6 months of competition is based on the pathophysiology of each virus and when serum levels are detectable. Discretion should be used for athletes with risk factors for contracting each virus, and the more frequent 3 months testing interval is recommended. For HIV, CD4+ lymphocytes start to decline 1 to 3 weeks after an infection. Conversely HIV-RNA increases during this time and reaches a peak at 6 weeks. Although HIV can be detected 10 days after initial infection, this would be impractical to low-risk individuals. HIV testing done at 3 months has been shown to be 99% accurate [37]. Testing should be done by a combination of antigen/antibody HIV-1/ 2 immunoassay (4th or 5th generation) followed by a confirmatory HIV-1/HIV-2 antibody differentiation immunoassay. If the antibody differentiation immunoassay is inconclusive then HIV-RNA testing needs to be done. Regarding HBV, serum with positive HBsAg, HBeAg and anti-HBc IgM levels indicate an acute infection and all of these peak at 3 months after infection in between the incubation phase and prodrome phase. During this time, it would be the best time to test athletes. Athletes should also be encouraged to be vaccinated against hepatitis B if they have not already done so.

For HCV, serum levels of anti-HCV peak at 2 - 3 months post infection. HCV should be tested via serum antibodies (anti-HCV). If positive, a follow-up PCR test to detect HCV-RNA is necessary to detect active infection. If a patient has been previously treated for HCV infection, then documentation of a completed treatment regimen and of SVR must be submitted. Confirmation of SVR requires negative serum anti-HCV testing at 12 weeks and 24 weeks after treatment.

Although it is recommended that fighters who test positive for HIV, Hepatitis B or C do not compete in combat sports, it is highly recommended that they continue to exercise. For patients with HIV, exercise has been shown to provide multiple benefits for patients living with HIV [130]. Exercise can enhance quality of life, cardiorespiratory fitness and mental health. Aerobic exercise especially, has been shown to improve in VO2max, lean body mass, and depression symptoms however no significant changes in CD4 count and viral load occur [131,132]. Like HIV, patients with Hepatitis B and C are encouraged to exercise to increase cardiorespiratory fitness, reduce inflammation, reduce incidence of heart disease and diabetes. Although exercise does not reduce viral load, it can have a positive long-term impact on the patient [133].

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