Human Immunodeficiency Virus Type 1

CAS No.: none assigned

Known to be a human carcinogen

Also known as HIV-1

Carcinogenicity

Human immunodeficiency virus type 1 (HIV-1) is known to be a human carcinogen based on sufficient evidence from studies in humans. This conclusion is based on epidemiological studies showing that HIV-1 increases the risk of Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervical cancer, invasive anal cancer, genital cancers (vaginal/vulvar and penile cancers), conjunctival eye cancer, and non-melanoma skin cancer, together with supporting evidence from mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence for an association between HIV-1 infection and oral-related (oral cavity and oropharyngeal), lung, and liver cancers.

The majority of these 12 types of cancer are considered to be related to co-infection with both HIV-1 and another cancer-causing virus. HIV-1 infection impairs the body's immune system so that it cannot adequately suppress or destroy cancer-causing viruses, resulting in an increased risk that these viruses will cause cancer in co-infected individuals. Discussion of the types of cancer associated with HIV-1 infection (below) is organized by whether or not they are related to co-infection with another virus (CDC 1992, Gopal *et al.* 2014, Patel *et al.* 2014). Three of the nine infection-related cancers (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical carcinoma) are types of cancer whose presence has been used to diagnose acquired immunodeficiency syndrome (AIDS) and are known as AIDS-defining cancers. AIDS is a disease caused by HIV-1 that attacks the body's immune system by reducing the number of CD4 T helper cells, which help the body fight off infection. Viral co-infections have not been identified for lung cancer, conjunctival eye cancer, or non-melanoma skin cancer; however, viral co-infection is likely involved in one type of non-melanoma skin cancer (Merkel cell carcinoma).

The impact on public health of HIV-1-related cancers is a major concern, as the excess number of cancer cases due to HIV-1 infection in the United States in 2010 was estimated to be over 3,900 (Robbins *et al.* 2015). In recent years, several studies have reported that HIV-1-infected individuals have increased risks for non-AIDS-defining cancers as a group, as well as for additional specific types of cancer, especially those not thought to be related to co-infection with other viruses (Shiels *et al.* 2009, Albini *et al.* 2013, Franzetti *et al.* 2013, Helleberg *et al.* 2015). Nonetheless, about 90% of the excess cancer due to HIV-1 infection identified by Robbins *et al.* is accounted for by the types of cancer described in this profile.

Infection-Related Cancers

Cancer Studies in Humans

Evidence for associations between HIV-1 infection and Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervical cancer, invasive anal cancer, vaginal/vulvar cancer, and penile cancer is based on consistent findings of statistically significant increased risk in numerous epidemiological studies in different populations. At least 30 cohort studies published through 2015 with relatively large numbers of HIV-1/AIDS cases (NTP 2016) found that people with AIDS or infected with HIV-1 had moderate to very high increased risks for most of these types of cancer, compared with the general population or with HIV-1-negative individuals. Although the general population may differ from HIV-1 infected individuals with respect to lifestyle-related risk factors for specific types of cancer (i.e., potential confounding factors), the overwhelming strength of the associations between these cancers and HIV-1 infection in numerous studies eliminates concern that the increased risks are explained by these potential confounding factors.

The evidence for vaginal/vulvar and penile cancers, which are rare, is based on a smaller number of studies (six or seven) for each type of cancer (Newnham *et al.* 2005, Mbulaiteye *et al.* 2006, Long *et al.* 2008, Patel *et al.* 2008, Chaturvedi *et al.* 2009, Dal Maso *et al.* 2009, Simard *et al.* 2010, Franzetti *et al.* 2013, Park *et al.* 2014, Raffetti *et al.* 2015). In general, similar risk estimates for penile cancer were found across different HIV-1 risk groups (injection drug users, heterosexuals, and men having sex with men), which helps to rule out potential confounding by lifestyle behaviors as the cause of the excess cancer risk observed in these studies (Chaturvedi *et al.* 2009).

For each type of infection-related cancer, the table below summarizes the level of evidence, the risk estimates from the studies, the cancer-causing virus with which the patients were infected, and whether the risk increased with low CD4 cell counts (which indicate impaired immune function) (NTP 2016).

There is limited evidence from studies in humans for a causal association between HIV-1 infection and oral-related cancer (oral-cavity and oropharyngeal cancers). At least 19 cohort studies found that HIV-1-infected people had 2- to 4-fold higher risks for oral-related cancer (all types combined, oropharyngeal cancer, or specific oral-cavity cancers) than did the general population or HIV-1-negative individuals; two studies reported risks over 10-fold higher for cancers of the tonsil or tongue (NTP 2016). Interpretation of these mod-

Type of cancer	Level of evidence	Risk estimates	Cancer-causing viral co-infection	Increased risk with low CD4 cell counts[a]?
Kaposi sarcoma	sufficient/AIDS-defining	100s to 10,000s	KSHV	Yes
Non-Hodgkin lymphoma	sufficient/AIDS-defining	10 to ~300	EBV, KSHV[b]	Yes
Hodgkin lymphoma	sufficient	4 to 38	EBV	Yes
Cervical	sufficient/AIDS-defining	2 to 22	HPV	Unclear; CIN = yes
Anal	sufficient	10 to 100	HPV	Yes
Vaginal/vulvar	sufficient	5 to 27	HPV	Yes
Penile	sufficient	4 to 28	HPV	Unclear
Oral-related	limited	2 to 4	HPV	Unclear
Liver	limited	2 to 16	HCV/HBV	Yes

CIN = cervical intraepithelial neoplasia; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HPV = human papillomavirus; KSHV = Kaposi sarcoma-associated herpesvirus.
[a]Low CD4 counts are a measure of an impaired immune system.
[b]Some types of non-Hodgkin lymphoma, primary effusion lymphoma, and the plasmablastic variant of multicentric Castleman disease.

estly increased risks is complicated by the fact that different subtypes of oral-related cancers, which were combined in most HIV studies, may develop by different mechanisms. The link between oral cancer and human papillomavirus (HPV) is likely to depend on the specific type of oral cancer. Risk factors (such as sexual activity) for HPV-related oropharyngeal cancer are thought to differ from those for non-HPV-related oral-cavity cancers (such as cigarette smoking and alcohol consumption) (Gillison *et al.* 2008). HPV-related cancers are more prevalent among HIV-1-infected than HIV-1-negative individuals, either because they differ with respect to risk factors for HPV or, possibly, because of the immunosuppressive effects of HIV-1 (Beachler and D'Souza 2013). In addition, most studies did not measure or control for other risk factors for oral cancer. In the only study identified that evaluated tobacco smoking, HIV-1 infection, and oropharyngeal cancer in HIV-1-positive and -negative individuals, controlling for smoking reduced the risk estimate from 1.9 to 1.4 (Silverberg *et al.* 2011).

Epidemiological studies also provide limited evidence for an association between HIV-1 infection and liver cancer (primarily hepatocellular carcinoma). At least 40 studies reported an increased risk (2- to 16-fold) of liver cancer among HIV-1-positive individuals; however, it is not possible to reasonably rule out the possibility that the excess risk can be explained by biases in these studies (NTP 2016). In the United States, hepatitis B virus (HBV) and hepatitis C virus (HCV) are more common among HIV-1-infected individuals than in the general population. Therefore, it is not clear whether HIV-1 infection is a potential confounding factor, because it is correlated with HBV or HCV infection, or whether it plays an active role in the development of HBV- and HCV-related liver cancer, primarily by suppressing the immune system. There is evidence to suggest that progression to end-stage liver disease or liver cancer is more aggressive in individuals co-infected with HIV-1 and HBV or HCV (Mohsen *et al*. 2002, Bourcier *et al.* 2012). In addition, several studies have found the risk of liver cancer to be associated with immune-system suppression, as measured by low CD4 cell counts, which would support a role for HIV-1 in cancer development (Engels *et al.* 2008, Guiguet *et al*. 2009, Silverberg *et al.* 2011, Vogel *et al.* 2011, Kramer *et al.* 2015). Some studies investigating the risk of liver cancer among individuals co-infected with HIV-1 and HCV have found no increased risk associated with HIV-1 co-infection or after controlling for HCV, arguing against a causal role for HIV-1 (Kramer *et al.* 2005, McGinnis *et al.* 2006, Di Benedetto *et al.* 2014). However, a limitation of these studies is that the cohorts may not have been followed up long enough for them to have developed liver cancer, which has a long period between initial exposure and development of cancer.

Studies on Mechanisms of Carcinogenesis

The available data support a mechanism of carcinogenesis in which an HIV-1-impaired immune system cannot adequately suppress or destroy cancer-causing viruses, resulting in increased risks of cancers caused by these viruses (NTP 2016). The risks of most (though not all) of the 12 types of cancer discussed above are related to decreased CD4 cell count; however, the relationships for the different types of cancer may depend on the timing of the decrease in CD4 cell count. In addition, high mortality from some types of cancer (such as cervical) during the early years of the AIDS epidemic, before the introduction of highly active antiretroviral therapy (HAART, more recently referred to as combined antiretroviral therapy, cART), might have masked the relationship between cancer risk and CD4 cell count (Chaturvedi *et al.* 2009). Abnormalities in cervical cells and an increased cancer risk from precancerous cervical lesions have been associated with low CD4 counts in several studies (Denslow *et al.* 2014).

HAART, which reduces the level of HIV-1 in the blood, has substantially decreased the risks of Kaposi sarcoma and non-Hodgkin lymphoma, supporting the link between HIV-1 infection and increased risk of these cancers. However, the cancer risks remain higher among HIV-1-infected individuals than among non-HIV-1-infected individuals (Shiels *et al.* 2011a,b). In contrast, the risks of Hodgkin lymphoma, invasive anal cancer, and possibly the genital cancers have increased with the advent of HAART, in part because people with HIV-1 now survive longer. This results in a larger and older population of HIV-1-positive individuals, thus increasing the chance that these types of cancer will develop and be observed. In addition, the toxicity of some of the antiretroviral drugs used in HIV-1/AIDS treatment may increase the risk of cancer (Borges *et al.* 2014). The effect of HAART is less clear for cervical cancer; some, but not all, studies have found decreased risk since the advent of HAART.

Impaired immune function alone clearly does not fully explain the incidences of cancer and range of cancer types observed among HIV-1-infected individuals either before or after the advent of HAART. Although HAART improves immune function and lowers the level of HIV-1 in the blood, it only partially reduces the inflammation associated with HIV-1 infection, suggesting that inflammation and other molecular pathways may contribute to the increased cancer risk (Borges *et al.* 2013, 2014). Some studies showed that cumulative or current levels of HIV-1 RNA in the blood were associated with an increased risk of AIDS-defining cancers independently of other risk factors, or that specific HIV-1 proteins (e.g., Tat and Vpr) might work synergistically with other cancer-causing viruses (Borges *et al.* 2014).

Cancers Not Known To Be Infection-Related

Cancer Studies in Humans

Evidence for associations between HIV-1 infection and conjunctival eye cancer and non-melanoma skin cancer is based on consistent findings of statistically significant increased risks in numerous epidemiological studies in different populations. The increased risks have ranged from moderate to high. The evidence for lung cancer is limited, because potential confounding from smoking could not be completely ruled out as the cause of lung cancer in these studies.

The evidence for an association of HIV-1 infection with conjunctival eye cancer comes from at least four cohort studies and four case-control studies (IARC 2012, NTP 2016) that reported positive associations, with relative risks ranging from 12 to 15 in most of the studies.

Over 15 studies have reported increased risks of non-melanoma skin cancer associated with HIV-1 infection, ranging mostly from 1.5- to 6-fold, but up to 20-fold in a few studies (NTP 2016). A meta-analysis that combined the findings of six cohort studies of people with HIV-1/AIDS published between 2003 and 2013 reported an overall relative risk of 2.76 (95% confidence interval = 2.55 to 2.98) (Zhao *et al*. 2015). In addition, a cohort study found a positive association between the level of HIV-1 RNA in the blood and the risk of non-melanoma skin cancer, suggesting an exposure-response relationship (Crum-Cianflone *et al.* 2015). Increased incidences of Merkel cell carcinoma, a rare form of non-melanoma skin cancer caused by Merkel cell polyomavirus (MCV), have been found in HIV-1-infected individuals in some studies (Engels *et al.* 2002), suggesting that this type of non-melanoma skin cancer can be considered an infection-related cancer. However, no studies have measured both MCV and HIV-1 viruses in Merkel cell carcinoma patients, so it is not known whether Merkel cell carcinoma is more likely to occur in people co-infected with both viruses than in those infected with a single virus.

The majority of studies (at least 48) have reported a positive association between HIV-1 infection and lung cancer (NTP 2016). Most of these studies reported statistically significant increased risks of approximately 1.5- to 6-fold. It has been suggested that tobacco smoking could explain the excess risk, because many of these studies compared lung cancer incidence between HIV-1-infected cohorts (with 40% to 80% smokers) and the general population, where the prevalence of smoking is typically much lower (20% to 40%). However, almost all studies that controlled for smoking (Phelps *et al.* 2001, Engels *et al.* 2006, Kirk *et al.* 2007, Shiels *et al.* 2010, Sigel *et al.* 2012, Hessol *et al.* 2015) or used statistical models to estimate the effect of smoking on cancer risk (Charturvedi *et al.* 2007) found the risks of lung cancer incidence or death to be at least doubled, and most of the increased risks were statistically significant. Although one study did not find an increased risk of lung cancer among the total HIV-1-infected population after adjusting for smoking (Silverberg *et al.* 2011), increased risks were found among those HIV-1-infected individuals whose blood had the highest levels of HIV-1 RNA (> 10,000 copies/mL) or lowest CD4 cell counts (≤ 200 cells/μL, the cutoff CD4 count for an AIDS diagnosis). The evidence suggests that tobacco smoking does not explain all of the excess risk of lung cancer among people infected with HIV-1. However, because smoking may not have been measured precisely in these studies, the possibility that smoking was the sole cause of lung cancer in these HIV-1-infected individuals could not reasonably be ruled out.

Studies on Mechanisms of Carcinogenesis

Mechanisms of carcinogenicity for these non-infection-related, non-AIDS-defining cancers are unclear, but (as with the AIDS-defining cancers) may be related to impaired immune function and inflammation in people infected with HIV-1 (NTP 2016). In addition, traditional risk factors (such as smoking, alcohol abuse, exposure to ultraviolet radiation, and age) may play a primary role in or contribute to the increased risk of non-AIDS-defining cancers in people with HIV-1 (Silverberg and Abrams 2007, Engels 2009, Shiels *et al.* 2011a, Borges *et al.* 2014). Furthermore, evidence is emerging for a direct carcinogenic effect of HIV-1 and some of its proteins, such as disruption of the cell-division cycle, inhibition of tumor-suppressor genes, promotion of chromosome instability, inhibition of DNA repair, and promotion of the carcinogenic effects of other agents (Borges *et al.* 2014).

Biological Properties

HIV-1 was first identified as the virus associated with AIDS in 1983. It is an enveloped single-stranded RNA retrovirus of the subfamily Orthoretrovirinae and genus *Lentivirus* (IARC 1996, 2012). HIV-1 is composed of an outer lipid membrane envelope with two surface proteins surrounding a protein matrix, inside of which is a protein capsid (shell) containing two copies of the 9.8-kb viral genome and the enzymes for viral replication, integration into host-cell genetic material, and processing of viral proteins.

HIV-1 infections are typically characterized by a long delay before the emergence of symptoms (IARC 1996, 2012, DHHS 2015). HIV-1 infects mainly CD4 cells, and also other cells of the immune system, including B cells, monocytes, macrophages, and follicular dendritic cells (IARC 1996, 2012). The immune system responds with increased production of CD8 (killer) T cells and antibodies that kill infected CD4 cells and other infected white blood cells. CD4 cells are also killed by viral replication and disruption of cell regulation. After an initial peak of infection, the amount of HIV-1 in the blood decreases (IARC 1996, 2012, CDC 2016a). The virus can then remain at low levels for 2 to 25 years, averaging about a decade, and can evade detection by the immune system through several mechanisms, including producing proteins that prevent the immune system from detecting the virus.

Detection

HIV-1 has been detected primarily in blood and sexual fluids (semen and vaginal secretions) and in very low concentrations in other body fluids, including saliva, urine, sweat, and tears (which may show higher concentrations if they have been contaminated by blood or sexual fluids) (IARC 1996, 2012). The most common detection methods have been based on detecting anti-HIV-1 antibodies by enzyme-linked immunosorbent assay, with confirmation by laboratory-based Western blot immunoassay or immunofluorescence assay for anti-HIV-1 antibodies (CDC 1989). Anti-HIV-1 antibodies typically cannot be detected by these methods until one to three months after infection (Hecht *et al.* 2011). Several more rapid and sensitive methods have been developed to screen for and confirm the presence of anti-HIV-1 antibodies, HIV-1 protein, and HIV-1 RNA in the blood. Some RNA-based detection methods also can measure HIV-1 in dried blood samples (Smit *et al.* 2014).

Exposure

A significant number of people living in the United States are infected with HIV-1. The current number is about 1.2 million, of whom an estimated 13% are unaware of their infection status (CDC 2015b). It is estimated that about 50,000 new HIV-1 infections occur in the United States each year. Although the incidence of new HIV-1 infections has remained stable over recent years, it varies considerably by risk group. Gay, bisexual, and other men who have sex with men, particularly young African American men, are most likely to be newly infected with HIV-1 (CDC 2012, 2015b).

AIDS typically results from long-term untreated HIV-1 infection. Approximately 65% of people newly diagnosed with HIV-1 remain untreated (the proportion varying by state of residence), accounting for 90% of new AIDS cases (CDC 2015c). About 1.2 million people in the United States have been diagnosed with AIDS since the start of the epidemic in 1981 (CDC 2015b). In 2013, 47,350 people were newly diagnosed with HIV-1 and 26,700 with AIDS. Since the start of the epidemic, about 660,000 people diagnosed with AIDS have died.

Transmission

HIV-1 is transmitted from one individual to another primarily during sexual activity (oral, anal, or vaginal), when HIV-1 in infected sexual fluids crosses mucous membranes to enter the bloodstream. Infection can also occur by direct blood-to-blood transmission, especially in certain populations, primarily through sharing of needles by injection drug users or, more rarely, by transmission through the skin, such as via needlestick injuries, or by the transfusion of infected blood (if the blood supply is not effectively screened for HIV-1) (IARC 2012). Because the U.S. blood supply and donated organs and tissues are screened for HIV-1, transmission via blood transfusion or organ transplant is expected to be rare (DHHS 2013). The estimated risk of infection via blood transfusion is about one in 1 million to 1.5 million per transfused unit (American Red Cross 2016). Screening of the U.S. blood supply began with a test for HIV-1/HIV-2 antibody in 1985, and nucleic acid testing for HIV-1 began in 1999.

Contact of nonsexual mucous membranes or broken skin with infected blood or body fluids by healthcare workers or first responders may also increase the risk of HIV-1 transmission (CDC 1987, Ippolito *et al.* 1999, Leiss *et al.* 2006); however, the risk of infection by these routes is estimated to be less than 1% (Cardo *et al.* 1997). Transmission of HIV-1 from mothers to children occurs *in utero,* through in-

fection of the child's mucous membranes during birth, or through breast milk.

The two primary behavioral risk factors for HIV-1 transmission in most developed countries are the practice of unprotected sex, particularly unprotected anal sex, and the sharing of needles used to inject drugs. Additional risk factors for HIV-1 infection include other sexually transmitted infections (such as chlamydia and gonorrhea), which can increase the risk of sexually transmitted HIV-1 infection in part by causing inflammation or rupture of mucous membranes in the vagina, vulva, penis, or anus. However, treatment or prevention of other sexually transmitted diseases does not always result in decreased HIV-1 infection rates (as reviewed by Ng *et al.* 2011). Other risk factors include circumcision and hormonal, immune, and genetic factors (IARC 1996, 2012).

Diseases (Non-Cancer), Prevention, and Treatment

The World Health Organization (WHO 2007) classifies four clinical stages of infection, from primary HIV-1 infection to AIDS. The CDC case definition for AIDS (CDC 1992, 1999) includes the presence of over 20 AIDS-associated infections or related conditions or a CD4 cell count in the blood of less than 200/μL, resulting in impairment of immune function (CDC 2015d). The most common non-cancer diseases associated with HIV-1 infection are those that most commonly occur in people with impaired immune systems. These include the fungal infections candidiasis, pneumocystis pneumonia, histoplasmosis, and cryptococcosis; the bacterial infections tuberculosis and mycobacterium avium complex; and the parasitic infections toxoplasmosis and cryptosporidiosis. A number of AIDS-related diseases are caused by viruses (such as cytomegalovirus and the cancer-causing viruses KSHV, EBV, and HPV, as discussed above) (IARC 1996, 2012, CDC 2015d). Some chronic conditions that are more common among HIV-1-infected than noninfected people (such as HIV-1-associated kidney disease) may result in part from long-term treatment with antiretroviral drugs, rather than from HIV-1 infection itself (Feeney and Mallon 2011).

With respect to prevention, behavioral risk-reduction strategies include education about safer sex practices (abstinence, consistent condom use, and testing for HIV-1 status), education about the risk of infection from contact of mucous membranes or broken skin with infected fresh blood, and the use of clean needles, particularly among high-risk populations, including sex workers, injection drug users, and infected pregnant mothers (CDC 2015a).

Effective screening of the blood supply and increased implementation of HIV-1 testing programs using rapid tests have reduced infection rates (CDC 2006). Starting short-term antiretroviral therapy soon after a high-risk exposure can prevent the establishment of HIV-1 infection, and pre-exposure treatment is now recommended for specific high-risk populations (CDC 2014). Early initiation of HIV-1 treatment has been shown to reduce the risk of transmitting HIV-1 to an uninfected partner by 96% (CDC 2016b). The risk of mother-to-infant HIV-1 transmission has been greatly reduced by treatment of the mother with antiretroviral drugs beginning before labor and continuing through breastfeeding, as well as by treatment of the infant immediately after birth and for up to 14 weeks among breastfed infants (Newell and Thorne 2004, UNAIDS 2013). Transmission has also been shown to be reduced by Caesarean delivery (European Mode of Delivery Collaboration 1999).

Treatment to reduce the viral load of HIV-1 consists of five main classes of antiretroviral drugs: fusion or entry inhibitors, integrase inhibitors, protease inhibitors, nucleoside/nucleotide reverse-transcriptase inhibitors, and non-nucleoside reverse-transcriptase inhibitors, which are designed to block various steps in the HIV-1 replication cycle (NIAID 2013). Combinations of these drugs (e.g., protease inhibitors and nucleoside reverse-transcriptase inhibitors) (HAART, or cART) are now incorporated into standard treatment guidelines (e.g., DHHS 2015).

A substantial international effort to develop an effective vaccine for HIV-1 has proved challenging (Wang *et al.* 2015), and no prophylactic or therapeutic vaccine is currently available. The National Institute of Allergy and Infectious Diseases Web site provides updated information on HIV vaccine research (NIAID 2015).

Regulations

Bureau of Prisons (BOP)

The BOP manages infectious diseases in the confined environment of a correctional setting through a comprehensive approach that includes HIV-1 testing.

The BOP may place an inmate who tests positive for HIV-1 in controlled housing status when there is reliable evidence that the inmate may engage in conduct posing a health risk to another person.

Victims of severe forms of human trafficking in federal custody shall receive necessary medical care and other assistance, including free optional testing for HIV-1 and other sexually transmitted diseases in cases involving sexual assault or trafficking into the sex industry.

Department of Defense (DoD)

If required by an agreement or local requirements, HIV-1 testing for deployment of contractors authorized to accompany the force in applicable contingency operations must occur within 1 year before deployment. The Combatant Command surgeon should be consulted in all instances of HIV-1 seropositivity before medical clearance for deployment.

Military health system personnel who provide or coordinate medical care for victims of sexual assault under the Sexual Assault Prevention and Response Program are required to consult with the victim, once clinically stable, regarding further healthcare options, including testing, prophylactic treatment options, and follow-up care for possible exposure to HIV-1 and other sexually transmitted diseases or infections.

Department of Health and Human Services (DHHS)

Designated states under the Substance Abuse Prevention and Treatment Block Grant program (i.e., any state whose rate of cases of AIDS is 10 or more per 100,000 individuals) must make early intervention services for HIV-1 disease, including testing to confirm the presence of the disease, available to individuals undergoing treatment for substance abuse.

Department of Homeland Security (DHS)

Aliens applying for temporary resident status or adjustment from temporary to permanent resident status are required to submit the result of a serologic test for HIV-1 virus.

Any alien inadmissible under Section 212(a)(1)(A)(i) of the Immigration and Nationality Act, as amended by the Immigration Reform and Control Act of 1986, because of HIV-1 infection may be issued a B-1 (business visitor) or B-2 (visitor for pleasure) nonimmigrant visa and be authorized for temporary admission into the United States for a period of 30 days subject to conditions in 8 CFR 4(f)(2).

Department of Housing and Urban Development (HUD)

HUD implements programs (e.g., Housing Opportunities for Persons with AIDS, Shelter Plus Care) designed to provide rental assistance for permanent housing and supportive services (including health care) for low-income individuals with HIV-1/AIDS and homeless persons with disabilities, including HIV-1/AIDS, and their families.

Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Department of Veterans Affairs (DVA)

For any record maintained in connection with the performance of any program or activity relating to infection with HIV-1, information may be disclosed to a federal, state, or local public health authority charged with protection of the public health under federal or state law, and to which federal or state law requires such disclosure, if a qualified representative of such authority has made a written request for such record pursuant to such law for a purpose authorized by such law.

A physician or professional counselor may disclose information indicating that a patient is infected with HIV-1 to the spouse of the patient or to an individual whom the patient has (during the process of counseling or of HIV-1 testing) identified as being a sexual partner of the patient.

Food and Drug Administration (FDA, an HHS agency)

Since May 2015, 21 CFR 606, 610, 630, 640, and 660 prescribe procedures, including recordkeeping, donor screening and notification, blood and blood component testing, and product labeling, to guard against the spread of HIV-1 through donation of blood, serum, or plasma.

21 CFR 1270 and 1271 prescribe procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products are free of HIV-1.

21 CFR 864 identifies class designations (Class I, II, or III) of analyte-specific reagents (e.g., analytes intended as components in tests intended for use in the diagnosis of HIV-1/AIDS) that determine the type of premarketing submission or application required for FDA clearance to market.

21 CFR 866 identifies the *in vitro* HIV-1 drug resistance genotype assay (a device intended for use in detecting HIV-1 genomic mutations that confer resistance to specific anti-retroviral drugs, as an aid in monitoring and treating HIV-1 infection) as a Class II medical device with special controls (i.e., a guidance document) requiring premarket notification for FDA clearance to market.

Patient examination and surgeon's gloves must be sampled and tested for leaks and other visual defects to reduce the risk of transmission of HIV-1.

The labeling of over-the-counter vaginal contraceptive and spermicide drug products containing nonoxynol-9 as the active ingredient must contain warnings that these products do not protect against the transmission of HIV-1/AIDS, may increase the risk of getting HIV-1/AIDS from an infected partner, and should not be used by individuals who have HIV-1/AIDS or are at high risk for HIV-1/AIDS.

Health Resources and Services Administration (HRSA, an HHS agency)

The recovery of organs for the purpose of transplantation from individuals infected with HIV-1 was prohibited beginning in 1988. However, an exception to this prohibition has been in place since 2013, when the transplantation of organs from HIV-1-positive donors was approved for recipients who were HIV-1-positive prior to receiving such organs.

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been developed for employers to develop and adhere to exposure control plans for bloodborne pathogens.

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Public Health Service (PHS, a division of HHS)

Programs or practitioners engaged in opioid treatment of individuals with an opioid agonist treatment medication must provide counseling on preventing exposure to and transmission of HIV-1 disease for each patient admitted or readmitted to maintenance or detoxification treatment.

Serologic testing for HIV-1 is required for aliens over 15 years of age who are applying for immigrant visas; are students, exchange visitors, or other applicants for nonimmigrant visas required by a United States consular authority to have a medical examination; are outside the United States applying for refugee status; or are in the United States applying for adjustment of their status under the immigration statute and regulations.

Guidelines

Centers for Disease Control and Prevention (CDC, an HHS agency)
National Institutes of Health (NIH, an HHS agency)
HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA)

The CDC, NIH, and HIVMA have issued federally approved HIV-1/AIDS medical practice guidelines.

Department of Defense (DoD)

DoD Instruction 6485.01 establishes policy, assigns responsibilities, and prescribes procedures for the identification, surveillance, and management of members of the military services infected with HIV-1 and for prevention activities to control transmission of HIV-1.

Department of Health and Human Services (DHHS)

DHHS has issued guidance regarding enrollment of children with disabilities (including HIV-1, AIDS-related complex, or AIDS) in Head Start programs. The guidance includes direction in the event that a child with disabilities presents a problem involving biting or bodily fluids.

DHHS has issued an updated Public Health Service guideline that prescribes donor screening and notification (e.g., recipient informed consent) procedures to guard against transmission of HIV-1 through organ transplants. This guidance also includes a revised set of risk factors for HIV-1 infection to help improve recipient informed consent and prompt more sensitive laboratory testing of donors and recipients when necessary.

Food and Drug Administration (FDA, an HHS agency)

The FDA has issued numerous guidance documents prescribing procedures (e.g., use of standardized labels, abbreviated donor screening questionnaires) for reducing the risk of virus transmission by blood and blood products.

Health Resources and Services Administration (HRSA, an HHS agency)

The Organ Procurement and Transplantation Network prescribes donor screening, recordkeeping, notification, and organ and vessel packaging, labeling, shipping, and storage procedures to guard against the spread of HIV-1 through solid (vascular) organ transplantation.

National Institutes of Health (NIH, an HHS agency)
Centers for Disease Control and Prevention (CDC, an HHS agency)

The NIH and CDC have published criteria for research involving transplantation of HIV-infected donor organs in HIV-positive recipients to (1) ensure that research using organs from HIV-positive donors is conducted under conditions protecting the safety of research participants and the general public and (2) ensure that the results of this research provide a basis for evaluating the safety of solid organ transplantation from HIV-positive donors to HIV-positive recipients.

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