

Vaccination in the person with newly diagnosed HIV



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Background

People living with human immunodeficiency virus (HIV) are at increased risk of acquiring multiple infections, many of which are preventable by vaccination. When an individual is newly diagnosed with HIV, it is important to take a vaccination history, test for immunity against a range of infectious diseases and administer vaccines as indicated, keeping in mind the person's immune status, as this may affect response to the vaccine, number of recommended doses and timing.

Objective

This aim of this article is to guide the general practitioner (GP) through each vaccine-preventable disease, highlight the risk in someone newly diagnosed with HIV and discuss the recommended number of doses and optimal timing of administration in relation to the individual's level of immunosuppression.

Discussion

The GP plays an important role in testing and diagnosing individuals with HIV. Prevention of disease is always preferable to treatment, and this article outlines an approach to vaccination that takes into account the variation in the level of immunosuppression that may be present at diagnosis and therefore affect an individual's responsiveness to a standard vaccine schedule.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) is a single-stranded RNA virus that is transmitted via infected bodily fluids. HIV primarily affects CD4+ T-cell number and function while also affecting other components of the immune system (eg macrophages, B cells and NK cells). This places people living with HIV at a higher risk of developing a number of infections, many of which are vaccine preventable (Table 1).

A patient with newly diagnosed HIV requires immediate referral to an HIV specialist who will assess the patient's suitability for antiretroviral therapy (ART) and initiate therapy as soon as it is safe to do so. The number of people choosing not to start treatment is currently very small. Vaccination may be delayed in this initial period while patients commence ART; however, an assessment of previous vaccination and serological protection to specific diseases should occur. A list of serology to consider is summarised in Table 2.

While there is substantial benefit in vaccinating people living with HIV, patients with CD4 counts of <200 cells/ μ L should not be administered live attenuated vaccines because of the risk of vaccine-related disease caused by active replication of the live vaccine virus. Patients with a CD4 count between 200 cells/ μ L and 350 cells/ μ L are moderately immunosuppressed, and clinical judgement should be used to guide the

administration of live vaccines in this cohort, balancing the risk of infection with the risk of adverse reaction to the vaccine. Another consideration in administering vaccines to a patient with newly diagnosed HIV is the response to the vaccine. A person who is immunosuppressed and has incomplete virological suppression may benefit from deferring vaccination. This is especially pertinent in the age of highly effective ART, which may facilitate immune reconstitution within a period of months and should be offered to all people with HIV irrespective of CD4 cell count or viral load.

This article outlines the vaccine-preventable conditions to consider for a person with newly diagnosed HIV. A detailed review of travel vaccines for people infected with HIV is beyond the scope of this article. Many of the listed vaccines are government funded, and general practitioners should refer to their respective health departments or the National Immunisation Program for up-to-date funding information.

Diphtheria, tetanus and pertussis

Corynebacterium diphtheriae and *Bordetella pertussis* are bacterial upper respiratory tract pathogens, while *Clostridium tetani* is a toxin-producing bacteria causing muscle spasm of varied severity. These infections are not considered to be more prevalent

or cause more severe disease in people with HIV, and vaccination should be administered in accordance with routine indications, regardless of immune status, viral load and ART.

Haemophilus influenzae serotype b

Haemophilus influenzae causes epiglottitis, pneumonia and meningitis after colonising the nasopharynx via droplet transmission. Invasive disease is caused by six capsulated serotypes, of which serotype b is the most virulent. The risk of invasive *Haemophilus influenzae* is increased in HIV affected people;¹ however, infection due to the vaccine strain (serotype b) is uncommon in settings where vaccine use is widespread.² Vaccination should be administered in accordance with routine indications.

Hepatitis A

Hepatitis A virus is transmitted via faecal-oral spread and causes acute hepatitis. People at increased risk include those who travel to high-risk countries, men who have sex with men (MSM), people who work in the sex industry, inmates of correctional facilities and people who inject drugs. Hepatitis A does not appear to be associated with worse clinical outcomes in people with HIV.³

Hepatitis A vaccination is recommended for all patients with HIV who have the aforementioned additional risk factors. The vaccine’s immunogenicity, while high, is correlated with CD4 cell count and viral suppression on ART.^{4,5} Recipients who received three doses (at zero, one and six months) were more likely to respond and have higher titres of hepatitis A virus antibodies when compared with recipients of two doses.^{6,7} A meta-analysis of five studies of people with HIV concluded that pooled seroprotection to hepatitis A virus was 92% after two years and 82% after five years.⁸

The single-antigen vaccine is recommended in two doses six to 12 months apart for people with a CD4 count >350 cells/μL. In people with a CD4 count <350 cells/μL, three doses are recommended at zero, one and six months.

Hepatitis B

The hepatitis B virus is transmitted via exposure to infected blood and body fluids, with infection occurring via vertical, sexual, parental or percutaneous routes. An estimated 5–10% of people with HIV are co-infected with chronic hepatitis B, with long-term sequelae such as cirrhosis and hepatocellular carcinoma occurring with increased frequency in co-infected patients.⁹ Hepatitis B vaccination is recommended for patients with HIV who have not been exposed to hepatitis B (ie those who are hepatitis B surface antigen [HBsAg] negative and hepatitis B surface antibody [HBsAb]

negative), especially those with risk factors for acquisition.

Hepatitis B vaccine is an inactivated vaccine, so it can be given at any CD4 count. There is no evidence that people with HIV have a higher rate of adverse events following hepatitis B vaccination. However, response rates to vaccination vary widely, with reduced response rates (as low as 33%) associated with a low CD4 cell count and high viral load at the time of vaccination.^{10–12} Given these data, it may be reasonable to delay vaccination until the patient with HIV is receiving ART and virologically suppressed with a CD4 cell count >200–350 cells/μL.

Table 1. Vaccination recommendations for adults with human immunodeficiency virus

Vaccine	Recommendation
Diphtheria, tetanus, pertussis	According to routine recommendations
<i>Haemophilus influenzae</i> type B	According to routine recommendations
Hepatitis A	Two doses (0, 6 months) for at-risk groups with CD4 >350 cells/μL Three doses (0, 1, 6 months) for at-risk groups if CD4 <350 cells/μL
Hepatitis B	Three doses (0, 1, 6 months) 40 μg if not immune Check HBsAb 4–8 weeks after final dose; if <10 IU, additional 1 × 40 μg dose
Human papillomavirus	Females <45 years and males <26 years Three doses (0, 1, 6 months)
Influenza	Annual
Measles, mumps, rubella	One or two doses if CD4 >200 cells/μL and not immune Not recommended if CD4 <200 cells/μL
Meningococcal ACWY	Two doses
Meningococcal B	Two doses (no clinical data but recommended)
Pneumococcal conjugate 13 (13vPCV)	One dose
Pneumococcal polysaccharide 23	One dose at least 12 months after 13vPCV Repeat dose five years later (two lifetime doses)
Varicella	Two doses if CD4 >200 cells/μL and IgG negative Not recommended if CD4 <200 cells/μL
Zoster	One dose if CD4 >200–350 cells/μL (and VZV IgG+) Not recommended if CD4 <200 cells/μL

HBsAb, hepatitis B surface antibody; IgG, immunoglobulin G; VZV, varicella-zoster virus

A meta-analysis of five studies concluded that high-dose hepatitis B vaccination (40 µg) provided increased HBsAb response rates when compared with standard dose vaccination (20 µg), with a pooled odds ratio of 1.96 (95% confidence interval: 1.47, 2.61).¹³ In a multicentre randomised controlled trial, a regimen of four high-dose (40 µg) vaccines at intervals of zero, one, two and six months was associated with superior seroconversion (82%) when compared with three 20 µg doses given at zero, one and six months (65%).⁷ However, an alternative strategy of three high-dose vaccines at zero, one and six months with an additional fourth dose of 40 µg if seroconversion (HBsAb >10 IU/L) has not occurred is a feasible alternative, with a retrospective study revealing that the regimen of three high-dose vaccines was efficacious in 83% of patients.¹⁴ Regardless of whether a three- or four-dose strategy is used, clinicians should check HBsAb 4–8 weeks after the final dose and repeat dosing (one further dose if three initial vaccines were given, or a repeated full course if four initial vaccines were given) if the HBsAb is <10 IU/L.

Human papillomavirus

Human papillomavirus (HPV) is an oncovirus responsible for causing genital warts as well as cervical, vulval, vaginal, penile, anal and oropharyngeal cancers. Two serotypes (HPV-6 and HPV-11) are responsible for the majority of noncancerous genital warts, and two serotypes (HPV-16 and HPV-18) are

associated with 60% of HPV-associated cancers.¹⁵ In one study, Australian men with HIV were almost twice as likely to carry the oncogenic HPV-16 serotype than homosexual men who do not have HIV (44.3%, compared with 25.4%).¹⁶ People with HIV have an increased rate of HPV infection, clinical disease and associated cancers; this risk is further increased in those with low CD4 cell counts and in MSM.^{16–18}

The original 4-valent HPV vaccine (4vHPV) developed in Australia was a virus-like particulate vaccine containing the major capsid (L1) protein of HPV types 6, 11, 16 and 18. The current 9-valent HPV vaccine (9vHPV) contains five additional serotypes (31, 33, 45, 52 and 58), which account for an extra 10% of HPV-related malignancies. Studies with the original 4vHPV vaccine have confirmed that it is both safe and immunogenic in people who are HIV positive across a wide age group.^{19–21} Vaccine-related antibody titres are increased for patients with a high CD4 count and low viral load, perhaps supporting deferring vaccination until patients are established on ART.²¹

In Australia, the vaccine is currently licensed for females ages 9–45 years and males aged 9–26 years. However, the vaccine may be offered to all people with HIV regardless of age, but the extent of individual clinical benefit is uncertain. The vaccine is administered at zero, one and six months; if interrupted, the course should be completed rather than restarted.

Influenza

The influenza virus causes respiratory illness and is a common cause of hospitalisation, morbidity and mortality in at-risk groups. Individuals with HIV infection are at greater risk of severe influenza and of complications, compared with other high-risk groups.^{22–24} Currently in Australia there are two available influenza vaccine types, the quadrivalent vaccine (for those <65 years of age) and an enhanced trivalent vaccine (for those >65 years of age). For those aged >65 years, the enhanced trivalent vaccine has been shown to induce higher serotype-specific antibody responses and reduce the likelihood of laboratory-confirmed influenza.²⁵ Higher rates of mild injection site reactions have been reported for elderly people, without an increase in systemic or serious adverse reactions.²⁶

Influenza vaccine antibody responses are lower for individuals with HIV when compared with individuals without HIV, and appears to correlate with lower CD4 cell counts and detectable viral loads.^{27–29} Administration of higher or more frequent doses has not been associated with improved immunogenicity.³⁰ Despite this, a recent meta-analysis of six studies showed a single-dose trivalent (non-enhanced) influenza vaccine prevented laboratory-confirmed influenza cases in 85% of adults with HIV.³¹ The influenza vaccine is recommended to be offered annually to all individuals with HIV regardless of immune status, viral load and ART.

Measles, mumps, rubella

The measles, mumps and rubella viruses cause a variety of febrile presentations, including conjunctivitis, coryza, maculopapular rash (measles, rubella) and salivary gland swelling (mumps). In patients with HIV, measles is associated with a higher mortality, with delayed and atypical presentations.³² The measles, mumps and rubella (MMR) vaccine contains live attenuated virus and is highly immunogenic in healthy subjects, with measles immunoglobulin G (IgG) developing in 90% of recipients after the first dose and 99% after two doses.³³ Fever and rash can occur as side effects in up to 15% of recipients.

Table 2. Serological tests to access vaccine requirement in patients with newly diagnosed human immunodeficiency virus

Serological test	Action
Hepatitis A IgG	Vaccinate at-risk groups if negative
Hepatitis B sAg + sAb	Vaccinate if not infected (sAg-) and not immune (sAb-)
Measles IgG	Vaccinate if CD4 >200 cells/µL and not immune
Mumps IgG	Vaccinate if CD4 >200 cells/µL and not immune
Rubella IgG	Vaccinate if CD4 >200 cells/µL and not immune
Varicella-zoster IgG	Vaccinate if CD4 >200 cells/µL and not immune

IgG, immunoglobulin G; sAb, surface antibody; sAg, surface antigen

The MMR vaccine is contraindicated for immunocompromised people as well as in pregnancy, and it should not be administered to patients with HIV who have a CD4 count of <200 cells/ μ L. For patients with HIV who are not immune to measles and have a CD4 count of >200 cells/ μ L, one or two doses of MMR are recommended depending on the number of doses received previously. Doses should be administered at least one month apart. As is the case with other vaccines, MMR responses in patients with HIV are reduced,³⁴ and immune reconstitution with ART appears to increase rates of measles IgG seropositivity post-vaccination.³⁵ Deferring vaccination until patients are established on ART should be considered in cases where the likelihood of exposure to measles is low. The MMR vaccine in combination with the varicella vaccine (MMRV) is not recommended.

Meningococcal disease

Neisseria meningitidis causes meningitis and bacteraemia, with a 5–24-fold increased risk for meningococcal disease among persons with HIV across multiple settings, with an associated higher mortality.³⁶

Currently available vaccines include the conjugate MenC and MenACWY (quadrivalent) vaccines as well as the recombinant MenB vaccine. All vaccines are immunogenic and induce serogroup-specific antibody responses. There appears to be a suboptimal response to a single dose of quadrivalent conjugate meningococcal vaccines in adolescents with HIV when compared with healthy controls.³⁷ Low CD4 count and non-suppressed HIV viral load were predictors of a poorer response.³⁸ No clinical data for individuals with HIV are available for MenB vaccine immunogenicity. Therefore, it is recommended that two doses of both MenACWY and MenB be administered eight weeks apart to adults living with HIV.

Pneumococcal disease

Streptococcus pneumoniae causes pneumonia and invasive disease. The rate of invasive pneumococcal disease (IPD) is

5–40 times higher in patients with HIV^{39,40} despite the use of ART,⁴¹ with mortality rates ranging from 0% to 33%,^{39–41} and up to 57% in those with bacteraemia in the pre-ART era.⁴² In addition to HIV, other risk factors for severe disease include low CD4 count, African American ethnicity, injecting drug use, smoking and alcoholism.⁴³

There are currently two pneumococcal vaccines licensed for adults in Australia: the conjugate vaccine containing 13 serotypes (13vPCV) and the polysaccharide vaccine containing 23 serotypes (23vPPV).

Pneumococcal conjugate 13 (13vPCV)

Conjugate vaccines are designed to elicit a T-cell dependent B-cell response resulting in superior memory B-cell formation and immunogenicity. In a previous study in Malawian adolescents and adults, two doses of a heptavalent pneumococcal vaccine (7vPCV) resulted in a vaccine efficacy of 74% against recurrent IPD caused by vaccine serotypes.⁴⁴ Multiple serological studies have confirmed significant increases in serotype-specific IgG and opsonophagocytic killing titres in patients with HIV (including those with low CD4 cell counts) after a single dose, with further doses providing little advantage for increasing antibody levels.^{45,46} A single dose of 13vPCV is recommended for all patients who are HIV positive regardless of CD4 cell count, 12 months after 23vPPV if this was given first.

Pneumococcal polysaccharide (23vPPV)

There is substantially reduced 23vPPV vaccine immunogenicity in HIV patients, particularly among those with low CD4 cell counts, when compared with young healthy controls.⁴⁷ Numerous observational studies have reported varying clinical effectiveness of 23vPPV from 20% to 79% against IPD, with factors associated with clinical failure including low CD4 count (<200 cells/ μ L) and viral load >100,000.⁴⁸ It is recommended that 23vPPV is administered at least 12 months after 13vPCV, with a repeated dose five years later.

Varicella-zoster virus

Chickenpox is caused by the varicella-zoster virus (VZV), which then remains latent within neurons. Reactivation of VZV causes shingles. In one study, the rate of VZV seronegativity among patients with HIV in the UK was 1.5%, with those acquiring primary infection more likely to present with severe disease.⁴⁹ The incidence rate of shingles in individuals with HIV remains 3–5 times higher than in individuals not infected with HIV. This elevated incidence remains even in the ART era and is associated with a low CD4 cell count and high viral loads. Patients with HIV have a higher incidence of cutaneous, neurological and visceral complications.⁵⁰

Chickenpox vaccine

The chickenpox vaccine is a live attenuated vaccine. It is not recommended for patients with a CD4 count of <200 cells/ μ L. In individuals with HIV who are not immune (VZV IgG negative) and have a CD4 count of >200 cells/ μ L, vaccination should be considered on the basis of safety and immunogenicity.⁵¹ It is recommended that two doses are given three months apart. The combination MMRV vaccine is not recommended.

Shingles vaccine

The currently available vaccine (Zostavax) is a more potent live attenuated vaccine designed to increase natural immunity and lower the incidence of shingles and post-herpetic neuralgia in those aged >50 years. Two doses were found to be safe and immunogenic in a trial of patients who were HIV positive with CD4 >200 cells/ μ L,⁵² and should be considered in those with CD4 counts of >200–350 cells/ μ L with serological confirmation of previous VZV infection. A new recombinant (non-live) zoster vaccine (Shingrix) has shown safety and efficacy in a cohort of patients with HIV, including a small number with a CD4 count between 50 cells/ μ L and 200 cells/ μ L.⁵³

Key points

- People with HIV are at higher risk of vaccine-preventable infections,

and newly diagnosed patients should be offered standard recommended vaccinations.

- Patients with CD4 counts of <200 cells/ μ L should not be administered live attenuated vaccines, and clinical judgement should be used to guide the administration of live vaccines in those with a CD4 count between 200 cells/ μ L and 350 cells/ μ L.
- Patients with a lower CD4 count (<200 cells/ μ L) and incomplete virological suppression generally have poorer vaccine responsiveness, and certain vaccines may be deferred until virological suppression is achieved.

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