



Routine vaccinations for HIV-1 infected adults

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This paper discusses common vaccines likely to be considered for routine (not travel- or epidemic-related) immunisation of HIV-1 infected adults in Australia. Several well reasoned discussions and recommendations regarding vaccination of HIV-1 infected adults have been written and the reader is referred to these also.(1,2)

Principles

1. In general, HIV-1 infected individuals should not receive any live viral or bacterial vaccines (eg. Measles/Mumps/Rubella, monovalent Rubella, BCG, yellow fever, oral Typhoid Ty21a, varicella-zoster, oral Polio, vaccinia). There have been instances of lethal infections with live vaccinia vaccines following vaccination of HIV-infected persons.(3) This principle however applies particularly to HIV-infected individuals with evidence of severe immunosuppression. Measles-mumps-rubella (MMR) vaccine for example is recommended for those without evidence of severe immunosuppression, and a recent update on recommendations for the use of yellow fever vaccine in asymptomatic HIV-infected individuals has recently been published.(4-6)
2. Immunisation of most HIV-infected individuals will cause a modest (approximately $0.5 \log_{10}$) rise in HIV-1 RNA levels. The rise in HIV-1 RNA levels is transient (about 4 weeks).(7) The clinical significance of this transient increase in HIV-1 replication is uncertain, but likely to be minimal. An analysis of an Amsterdam cohort did not show a significant change of HIV progression associated with vaccines, although this was performed in an era prior to the availability of effective antiretroviral therapy.(8) Adequate antiretroviral treatment will blunt the increase in HIV-1 replication but probably not ameliorate it all together. To date there have not been reports of development of HIV-1 resistance associated with rises in HIV-1 RNA levels following vaccination of individuals on antiretroviral therapy. In an SIV/maaque model, T cell activation associated with BCG or PPD exposure was shown to result in increased genetic diversity of SIV in vivo.(9) Substantially greater rates of genetic diversity (and potential induction of antiretroviral resistance) would most likely be induced by vaccine-preventable infections compared to vaccination, although the comparative risk has not been quantified.
3. Response to vaccination of HIV-infected individuals is suboptimal compared to HIV-uninfected individuals.(10) Response to vaccination decreases with falling CD4 cell counts (especially $<100/\mu\text{l}$), symptomatic HIV-1 infection and probably high HIV-1 RNA levels.(6) Vaccinations are most immunogenic when given to asymptomatic patients with higher CD4 cell counts and lower HIV-1 RNA levels. Whether rises in CD4 cell counts and reduction in HIV-1 RNA levels induced by antiretroviral therapy will result in greater immunogenicity of vaccines is unknown, although recovery of other immune parameters such as CMV-specific immunity suggest this is likely.(11) It is reasonable to recommend, pending further data, that if combination antiretroviral therapy is going to be instituted in the near future and the individual likely to return for follow up, vaccinations could be delayed until a few months following therapy when a better response is more likely to be achieved.



Recommended vaccines

1. Hepatitis B vaccine

A course of hepatitis B vaccination should be given to all hepatitis B non-immune HIV-infected persons. HIV-infected persons (regardless of route of transmission) are at a higher risk of both contracting hepatitis B infection and becoming chronic hepatitis B carriers. HIV-HBV coinfection results in higher rates of progression to chronic hepatitis B.(12,13)

2. Hepatitis A vaccine

A course of hepatitis A vaccination should be given to all HIV-infected, hepatitis A non-immune individuals. The majority of people with HIV in Australia are homosexual or bisexual men, injecting drug users, or partners of these individuals and are therefore at high risk of hepatitis A infection.(14)

3. Measles-mumps-rubella (MMR) vaccine

Most adults are likely to be immune to measles and it is not likely that MMR vaccination would be indicated for many HIV-infected adults. However, in light of recent outbreaks of measles in Australia, this issue does need to be considered.(15, 16) Immunity to measles is lowest, 74%, in those born between 1975 and 1981.(17) No serious adverse events have been reported in asymptomatic HIV-infected persons after measles vaccination, therefore it is recommended that adults who are not immune to measles should be vaccinated if their HIV disease is asymptomatic or do not have evidence of severe immunosuppression.(5, 6) It should be noted however that there has been one report of a serious complication of the measles vaccine (fatal giant-cell pneumonitis was reported in a severely immunosuppressed adult with HIV).(3,18)

Vaccines which should be considered

1. Influenza vaccine

There is little evidence to date that influenza infection is either more common, more severe, or associated with enhanced HIV progression in HIV-1 infected individuals compared to controls. Some infections (eg. CMV disease, tuberculosis) have been associated with accelerated HIV-1 disease progression, however these infections generally either only complicate already progressive HIV-1 infection or are chronic infections, unlike influenza.(19, 20) None-the-less, it remains possible that influenza infection could accelerate HIV-1 disease progression in a subset of infected persons.

The efficacy of influenza vaccination of HIV-1 infected individuals is unknown but likely to be low in persons with advanced disease.(21, 22) A reduced antibody response is seen in HIV-infected individuals compared to controls, with a significant correlation between antibody response and CD4 cell count.(23, 24) Those with a CD4 cell count <100/ml have a severely impaired antibody response. Efficacy would also depend on the success in predicting circulating strains in a given year. Presumably the increase in HIV replication associated with influenza infection would be greater than that associated with yearly vaccination, but the magnitude of the difference is unknown.(25, 26) There have been many conflicting results reported regarding increases in plasma HIV RNA levels following immunisation with some studies reporting an increase in HIV expression and others showing no increase.(23) When increases in viral load are seen, they are usually transient. A recent publication of data from the Adult and Adolescent spectrum of HIV disease Surveillance (ASD) Project in the United States found that influenza vaccination was not associated with change in CD4 cell count or HIV RNA level 3-12 months after vaccination. There was also no evidence that influenza vaccination was associated with increased progression to HIV disease or to death among persons with HIV infection.(27) The theoretical risk of enhancing HIV-1 progression of annual vaccinations versus an averted episode of influenza infection is highly speculative. Natural influenza infection imparts more effective and durable immunity in HIV-uninfected humans than does vaccination, but this has not been demonstrated in HIV-infected individuals. In the absence of more compelling data, yearly influenza vaccination should be discussed with each individual HIV-infected patient. HIV-1 infected individuals at risk of complications of influenza infection due to advanced age, chronic respiratory or cardiovascular disease should receive influenza vaccination. Contact with large numbers of the public or other HIV-infected persons might be one factor to consider, although there is little data that this imparts a substantially higher risk of acquisition or spread of the infection. In an epidemic year, vaccination should be more strongly considered. Prophylaxis and early treatment with amantadine/rimantidine and early treatment with neuraminidase inhibitors should also be considered.



2. Tetanus/diphtheria/pertussis

In general, HIV-infected adults should be revaccinated with adult diphtheria/tetanus vaccine as for HIV-uninfected adults. The 2000 NHMRC guidelines no longer recommend regular booster doses at 10 yearly intervals as immunity following complete vaccination is long lasting. A booster dose is recommended at age 50. Older adults who have not received a dose at age 50 should receive a booster vaccination if more than 10 years have elapsed since the last dose.(28) The risk of diphtheria or tetanus disease is however extremely low and many practitioners may wish to discuss the balance between the risk of disease acquisition and vaccine-induced transient HIV replication with their patients. Adult pertussis infection is becoming more common in Australia(29), although there is no evidence to date that adult pertussis infection is either more common, more severe, or associated with enhanced HIV progression in HIV-1 infected individuals compared to controls. If pertussis vaccination is considered, it might be prudent to use acellular pertussis vaccines since the decreased reactogenicity compared to the cellular pertussis vaccine is likely to be associated with smaller rises in HIV-1 RNA levels.(30)

Vaccines not recommended

Pneumococcal vaccine

HIV infected individuals have a high rate of pneumococcal disease and *S. pneumoniae* has increasing antibiotic resistance.(31) A recent randomised placebo controlled trial in Ugandan adults showed that 23-valent pneumococcal polysaccharide vaccination resulted in no reduction in pneumococcal disease or mortality, but an increase in pneumonia of all causes.(32) Adjusted analysis of first pneumonic events showed a hazard ratio of 2.02 (95% CI 1.19-3.42, p=0.008) for the vaccine group compared to placebo. Although a different setting than Australia based on this single well conducted randomised study, pneumococcal vaccination can no longer be unreservedly recommended for HIV-infected adults. In contrast to that study, a retrospective case control study in the USA showed significant protection from vaccination, particularly in Caucasians.(33) Overall vaccine efficacy was 49% (95% CI 12%-70%) and in whites, vaccine efficacy was 76% (95% CI 35%-91%). However, patients with pneumonia of unknown aetiology (potentially including pneumococcal pneumonia) were not excluded as controls, and therefore efficacy of the vaccine may have been overestimated. CD4 count at the time of vaccination was also not known for this study. Other studies have only shown vaccine efficacy in those with a CD4 count >500/ml at the time of vaccination.(34) Randomised studies in developed countries are clearly needed to make a firm recommendation, however given that the recommendation is still in current published guidelines and that large numbers (>20 000 person years of follow-up) would be required to adequately power such a study, such data are unlikely to be available soon. Newer conjugate pneumococcal vaccines will become available shortly, which may be more immunogenic, however one study has shown no significant difference in antibody response between this and pneumococcal polysaccharide vaccine in HIV-infected patients.(10)

Other considerations

Varicella vaccine

The use of varicella vaccine in individuals infected with HIV has not been studied, and therefore it is recommended that these patients not be vaccinated. Although these are guidelines for the use of vaccinations in HIV-infected adults, it seems prudent to mention the recommendation for consideration of the use of varicella vaccine in some HIV-infected children.(35) Data from a study of 41 asymptomatic or mildly symptomatic (CDC stage N1 or A1) HIV-infected children immunised with two doses of varicella vaccine demonstrated the vaccine to be safe, and no child developed proven varicella or zoster in two years of follow-up. On the basis of these results, the vaccine should now be considered for use in HIV-infected children who have no clinical or laboratory evidence of significant immunosuppression.

In addition, herpes zoster in HIV-infected children is somewhat different to that in HIV-infected adults. The incidence of zoster in children is much higher than in adults, particularly in those children who develop varicella in the setting of severe immunodeficiency. Incidence rates per 100 person-years of observation are reported as: 51(adults with HIV after varicella), 30 (children with varicella after HIV and CD4 cells >20% at varicella) and 467 (children with varicella after HIV and CD4 cells <20% at varicella).(36) Lower incidence rates of zoster following vaccination compared with natural varicella infection have been demonstrated.(37) It is possible that varicella vaccination may prevent or modify zoster by boosting CMI to VZV and open-label pilot studies in HIV-infected children and adults with a history of varicella are under way.(38)



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