Learning Objectives

After attending this presentation, learners will be able to:

▪ Apply updated guidelines on immunizations in persons living with HIV infection in their practice
▪ Describe the role of several vaccines in STI and cancer prevention
▪ Identify the potential role of a new Hepatitis B vaccine in HIV care
▪ List the expanded indications for the HPV vaccine

Vaccines are Available for 28 Infectious Diseases

- Adenovirus
- Anthrax
- Cholera
- Dengue
- Diphtheria
- H. influenzae infection
- Hepatitis A
- Hepatitis B
- Herpes zoster
- HPV infection
- Influenza
- Japanese Encephalitis
- Measles
- Meningococcal Disease
- Monkeypox
- Mumps
- Pertussis
- Pneumococcal Disease
- Polio
- Rabies
- Rotavirus infection
- Rubella
- Smallpox (Vaccinia)
- Tetanus
- Tuberculosis (BCG)
- Typhoid Fever
- Varicella
- Yellow Fever
### HIV Adult Immunization Schedule by Vaccine and Age Group, September 2019

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19-35 yrs</th>
<th>27-64 yrs</th>
<th>&gt; 65 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>1 dose annually</td>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td>Td/Tdap</td>
<td>Substitute Tdap for Td once, then Td booster every 10 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella*</td>
<td>2 doses (3 months apart if CD4 &gt; 350 cells/mm³ and no immunity to Varicella)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>3 doses (0, 2, and 6 months)</td>
<td>2 doses (0 and 6 months)</td>
<td></td>
</tr>
<tr>
<td>Zoster Recombinant</td>
<td>2 doses at 0 and 2-6 months, &gt; 55 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster Live*</td>
<td>1 dose if CD4 &gt; 200 cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR*</td>
<td>2 doses of 2 doses Td or Tdap and no immunity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV-13</td>
<td>1 dose, preferably prior to PPSV-23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPSV-23</td>
<td>2 doses 5 years apart, at least 8 weeks after PCV-13</td>
<td>1 dose</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2 doses depending on vaccine (2 doses if no immunity)</td>
<td>1 dose</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2 or 3 doses depending on vaccine. Check HIV status after.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal Conjugate</td>
<td>1 dose of either MenACWY or MenACWY-CRM 85</td>
<td>1 dose</td>
<td></td>
</tr>
</tbody>
</table>

*After assessing age, presence of immunity, and CD4 count. High dose flu vaccine is my recommendation. Recombinant zoster vaccine is preferred over the live zoster vaccine. Live vaccines (MMR, Varicella, Zoster Live, and Yellow Fever) should not be given if CD4 < 200 cells/mm³. The oral typhoid and live flu vaccines are contraindicated in HIV.

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### Vaccines to Prevent STIs

- Vaccines for diseases clearly linked to sexual transmission and discussed in the CDC STD Treatment Guidelines
  - Hepatitis A vaccine
  - Hepatitis B vaccine
  - Human papillomavirus vaccine

- Vaccines for diseases where close intimate or non-intimate contact could facilitate transmission of the disease
  - Meningococcal vaccines

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### Hepatitis A Epidemiology in the U.S.

Incidence of hepatitis A, by year
United States, 2000-2016

https://www.cdc.gov/hepatitis/hav/havfaq.htm#general
State-Reported Hepatitis A Outbreaks as of August 9, 2019


Hepatitis A: Indications for Vaccine

- Not at risk but want protection from Hepatitis A
- At risk for Hepatitis A
  - Chronic liver disease
  - Clotting factor disorders
  - Men who have sex with men
  - Injection or non-injection drug use
  - Homelessness
  - Work with hepatitis A viruses
  - Travel in countries with high or intermediate endemic hepatitis A
  - Close personal contact with international adoptee

https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html#note-hepa

From the IDSA HIV Primary Care Guidelines

- Hepatitis A vaccination is recommended for all susceptible men who have sex with men, as well as others with indications for HAV vaccine (e.g., injection drug users, travelers to countries of high endemicity, persons with chronic liver disease, or who are infected with hepatitis B and/or C).
- Vaccination can be considered for all nonimmune patients

Hepatitis A Vaccines: Recommended Dosages and Schedules

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age Group</th>
<th>Volume</th>
<th># Doses</th>
<th>Dosing Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV vaccine (either formulation)</td>
<td>19 years and older</td>
<td>1.0 mL</td>
<td>2</td>
<td>0, 6-12 months</td>
</tr>
<tr>
<td>HAV/HEV combination vaccine</td>
<td>18 years and older</td>
<td>1.0 mL</td>
<td>3</td>
<td>0, 1 month, 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 mL</td>
<td>4</td>
<td>0, 7 days, 21-30 days, 12 months</td>
</tr>
</tbody>
</table>

Adapted from table at www.immunize.org

Hepatitis A: Post-exposure Prophylaxis

- Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of monovalent hepatitis A vaccine or IG (0.02 mL/kg) as soon as possible, ideally within 2 weeks of exposure because the efficacy of vaccine or IG or vaccine when administered >2 weeks after exposure has not been established.

- If IG is administered to persons for whom hepatitis A vaccine also is recommended, a dose of vaccine should be provided simultaneously with IG, and the second vaccine dose should be administered according to the licensed schedule to complete the series. The combined vaccine can be considered in persons for whom both hepatitis A and hepatitis B vaccine is recommended.

Nelson N, et al. MMWR November 2, 2018;67(43):1216-1220

Incidence of Hepatitis B in the U.S.
ARS Question 1: An HIV+ patient with a CD4 count of 180 cells/mm$^3$ is s/p 3 doses of the Hepatitis B vaccine. Hepatitis B surface antibody testing is negative. What is your next step?

A. Give a booster dose of the standard Hepatitis B vaccine and recheck HBsAb level
B. Repeat the standard 3-dose Hepatitis B vaccine series and recheck HBsAb level
C. Administer the higher dose Hepatitis B vaccine often used in hemodialysis patients and recheck HBsAb level
D. Administer the 2-dose series of the recombinant Hepatitis B vaccine with a novel adjuvant

Hepatitis B Vaccines: Recommended Dosages and Schedules

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age Group</th>
<th>Volume</th>
<th># Doses</th>
<th>Dosing Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard recombinant Hepatitis B vaccine (either formulation)</td>
<td>20 years and older</td>
<td>1.0 mL</td>
<td>3</td>
<td>0, 1-2 months, 4-6 months</td>
</tr>
<tr>
<td>Recombinant Hepatitis B vaccine with a novel adjuvant</td>
<td>18 years and older</td>
<td>0.5 mL</td>
<td>2</td>
<td>0, 1 month</td>
</tr>
<tr>
<td>HAV/HBV combination vaccine</td>
<td>18 years and older</td>
<td>1.0 mL</td>
<td>3</td>
<td>0, 1 month, 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 mL</td>
<td>4</td>
<td>0, 7 days, 21-30 days, 12 months</td>
</tr>
</tbody>
</table>

Adapted from table at www.immunize.org

Advice on Hepatitis B Vaccination in HIV Infection

- In patients who present to care with a lower CD4 cell count, vaccination should not be deferred until CD4 counts increase to >350 cells/mm$^3$ because some patients with HIV infection with CD4 counts <200 cells/mm$^3$ do respond to vaccination (AII).
- Among persons with HIV infection who did not respond (anti-HBs titers <10 IU/mL) to a primary 3-dose vaccine series with a recombinant vaccine, 25% to 50% responded to an additional vaccine dose, and 44% to 100% responded to a 3-dose revaccination series. As a result, persons with HIV infection who do not respond to a complete hepatitis B vaccination series with one of the recombinant vaccines should receive a 3-dose revaccination series (BIII).


New York, New York, September 12, 2019
Advice on Hepatitis B Vaccination in HIV Infection

- Some specialists might delay revaccination until antiretroviral therapy (ART) results in a sustained increase in CD4 cell count (CIII).
- Two randomized controlled trials have shown that using 4 doses of double-dose of the recombinant vaccine produces higher anti-HBs titers than 3 doses of standard-dose vaccine, and one study also showed a higher overall response rate.

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.


New Hepatitis B Vaccine with a Novel Adjuvant

- Approved by the FDA in November of 2017 for persons 18 and older
- Contains a novel adjuvant, CpG 1018
- 2-dose series separated by 1 month
- In clinical trials that led to licensure, the seroprotection rate (anti-HBs of 10 mIU or higher) was achieved in 90-95% of subjects receiving this 2-dose series compared to 65-81% of those receiving 3 doses a standard recombinant Hepatitis B vaccine

Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant. MMWR April 20, 2018;67(15);455-458

What do the DHHS OI Guidelines say?

- In four randomized-controlled trials, the recombinant Hepatitis B vaccine with a novel adjuvant (2-dose series) was superior a standard recombinant Hepatitis B vaccine (3-dose series) in HIV-negative individuals.
- In the largest trial, the protection rate was 95% for the 2-dose series and 81% for the 3-dose series. There was an increase in the number of cardiovascular events in the 2-dose series group that was not statistically significant.
- The safety and efficacy of the 2-dose series in individuals with HIV infection has not been studied. If a two-dose vaccine is preferred, a recombinant Hepatitis B vaccine with a novel adjuvant is an option (CIII).

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

Passive Immunization (Immunoglobulin) in Hepatitis B

- Both passive-active PEP (the simultaneous administration of HBIG [i.e., 0.06 mL/kg] and hepatitis B vaccine at separate sites) and active PEP (the administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV. HBIG alone also has been demonstrated to be effective in preventing HBV transmission, but with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination.

Protective Effect of Hepatitis B Virus-Active Antiretroviral Therapy Against Primary Hepatitis B Virus Infection

- Retrospective cohort study of 2,942 HIV+ persons.
- 381 men identified with negative Hepatitis B serologies with a second serology available for evaluation
- Over incidence rate of Hepatitis B was 1.1 per 100 person-years
- 2.85 per 100 person-years if not on Hepatitis B active drugs
- 1.36 per 100 person-years if on lamivudine as the only Hepatitis B active drug
- 0.14 per 100 person-years if on tenofovir


ARS Question 2: In my HIV clinical practice, I provide the HPV Vaccine to the following persons:

A. Women up to age 26 and men up to age 21
B. Women and men up to age 26
C. Women and men up to age 45
D. All persons living with HIV infection regardless of age
E. None of the above
Impact of HPV in the U.S.

- An estimated prevalence of 79 million persons in the U.S.
- An estimated incidence of 14 million cases each year
- Over 40,000 HPV-associated cancers in 2015 including cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers
- 80% of HPV-associated cancers are due to HPV types 16 or 18
- However, 12% are attributable to other HPV types (31, 33, 45, 52, and 58) that are contained in the 9-valent vaccine

Human Papillomavirus (HPV) Infection

- Over 150 HPV types
- 40 HPV types can cause anal or genital warts
- HPV-related Cancers
  - Cervical
  - Vaginal
  - Vulvar
  - Penile
  - Anal
  - Oropharyngeal

Incidence of Non-AIDS Cancers among HIV + Persons Compared to General U.S. Population (Excludes Cervical Cancer which is AIDS-Defining)

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Standardized Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal Cancer</td>
<td>42.9</td>
<td>34.1 - 53.3</td>
</tr>
<tr>
<td>Vaginal Cancer</td>
<td>21</td>
<td>11.2 - 35.9</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>14.7</td>
<td>11.6 - 18.2</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>7.7</td>
<td>5.7 – 10.1</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>3.3</td>
<td>2.8 – 3.9</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.6</td>
<td>1.9 – 3.6</td>
</tr>
<tr>
<td>Oropharyngeal Cancer</td>
<td>2.6</td>
<td>1.9 – 3.4</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>2.5</td>
<td>1.6 - 3.8</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>2.3</td>
<td>1.8 – 2.9</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>1.8</td>
<td>0.4 – 0.8</td>
</tr>
</tbody>
</table>

Timeline of HPV Vaccine Development

- 2006: Approval of 4-valent HPV vaccine in adolescents and young men and women
- 2009: Approval of 2-valent HPV vaccine
- 2014: Approval of 9-valent HPV vaccine
- 2017: The 9-valent vaccine becomes the only available vaccine in the U.S.
- 2018: FDA approval to expand the age range of the 9-valent vaccine to persons aged 27-45 years
- 2019: ACIP recommendations published for use of the vaccine in some persons aged 27-45 years

HPV Vaccine for Persons 27 to 45

- On 10/5/18, the FDA approved the expanded use of the Human Papilloma Virus 9-valent vaccine to men and women aged 27 to 45 years.
- On 6/27/19, the ACIP recommend the use of this vaccine in persons aged 27 to 45 years with shared decision-making with their provider.
- On 8/16/19, this recommendation was published in the MMWR which should allow the expanded use and coverage by payers.

- For adults aged 27-45 who are not adequately vaccinated, clinicians can consider discussing HPV vaccination with persons who are most likely to benefit. Some points to consider:
  - Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk.
  - At any age, a new sex partner is a risk for a new HPV infection.
  - Most sexually active persons have been exposed to some HPV types, although not necessarily all of the types in the vaccine.
  - HPV vaccines do not prevent progression of HPV infection, decrease time to HPV clearance, or treat HPV-related disease.

Meningococcal Disease in HIV Infection

- In a surveillance system in the U.S. of approximately 43 million persons, 62 cases of meningococcal disease were reported in HIV+ persons from 1995-2014
- The incidence for persons with HIV has been estimated at 3.4-6.6 cases per 100,000 with a relative risk 5-13 fold above the general population
- A low CD4 count or high viral load has been associated with an increased risk
- 2016 guidelines from ACIP recommend the use of meningococcal conjugate vaccines in all persons living with HIV infection


Recommended meningococcal conjugate vaccination schedule and intervals for HIV-infected persons — ACIP, United States, 2016

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommended Schedule and Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 years</td>
<td>4 doses of MenACWY-CRM at ages 2, 4, 6, and 12–15 months 2 doses of MenACWY-D at age 9–23 months, 12 weeks apart</td>
</tr>
<tr>
<td>2 years</td>
<td>2 doses of MenACWY-O or MenACWY-CRM, 8–12 weeks apart</td>
</tr>
<tr>
<td>Booster Dose</td>
<td>Additional dose of MenACWY-D or MenACWY-CRM 3 years after primary series; boosters should be repeated every 5 years thereafter</td>
</tr>
<tr>
<td>&gt; 7 years</td>
<td>Additional dose of MenACWY-D or MenACWY-CRM 5 years after primary series; boosters should be repeated every 5 years thereafter</td>
</tr>
</tbody>
</table>

- Lower immunogenicity seen in HIV+ persons with CD4 < 15%
- MenACWY is recommended for HIV-infected persons aged ≥56 years because of the need for revaccination (i.e., booster doses).


Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

- Retrospective case-control study at sexual health clinics
- Persons aged 15-30 eligible to receive MeNZB and diagnosed with gonorrhoea, Chlamydia, or both
- 14,730 cases and controls
- Vaccinated individuals were significantly less likely to be cases than controls (511 [41%] vs 6424 [51%]; adjusted OR 0.69 [95% CI 0.61–0.79]; p<0.0001).
- Estimated vaccine effectiveness of MeNZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39).

Vaccines are also Important for Travel

- Persons living with HIV infection may travel overseas
- STDs may be acquired during travel
- Certain vaccines are indicated for certain destinations:
  - Cholera: Selected destinations with outbreaks and anticipated contact
  - Hepatitis A: Many parts of Central and South America, Mexico, Africa, and Asia
  - Hepatitis B: If not immune, most destinations where sexual activity is planned
  - Influenza: All destinations
  - Japanese Encephalitis: Parts of Asia
  - Meningitis: Parts of Africa
  - Polio: Rarely given although there is still polio in Nigeria, Afghanistan, and Pakistan
  - Rabies: Many destinations where the trip is prolonged or animal exposure is likely
  - Typhoid: Many parts of Central and South America, Mexico, Africa, and Asia
  - Yellow Fever: Parts of Africa and South America

Timing of Vaccination In Relationship to CD4 Lymphocyte Count in Persons with HIV Infection

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Comments Regarding CD4 Count</th>
<th>Source of Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Give regardless of CD4 count</td>
<td>Adult Immunization Schedule</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Give regardless of CD4 count;</td>
<td>Adult Immunization Schedule</td>
</tr>
<tr>
<td></td>
<td>in non-responders can delay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vaccination if CD4 &lt; 100 cells/mm</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>Give regardless of CD4 count</td>
<td>Adult Immunization Schedule</td>
</tr>
<tr>
<td>Polio</td>
<td>Give before departure; see</td>
<td>Adult Immunization Schedule</td>
</tr>
<tr>
<td></td>
<td>MMWR for specific destinations</td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>Encephalitis: Parts of Asia</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>Parts of Africa</td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>Rarely given although there</td>
<td></td>
</tr>
<tr>
<td></td>
<td>is still polio in Nigeria,</td>
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<td></td>
<td>Afghanistan, and Pakistan</td>
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<tr>
<td>Rabies</td>
<td>Many destinations where the</td>
<td></td>
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<tr>
<td></td>
<td>trip is prolonged or animal</td>
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<tr>
<td></td>
<td>exposure is likely</td>
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<tr>
<td>Typhoid</td>
<td>Many parts of Central and</td>
<td></td>
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<td></td>
<td>South America, Mexico, Africa,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and Asia</td>
<td></td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Parts of Africa and South</td>
<td></td>
</tr>
<tr>
<td></td>
<td>America</td>
<td></td>
</tr>
</tbody>
</table>

Summary

- Vaccines play an important role in HIV primary care and are available for several sexually transmitted infections including Hepatitis A, Hepatitis B, and HPV infection
- Hepatitis A vaccination is of increasing importance given the current outbreaks in the U.S.
- A new formulation of Hepatitis B vaccine has promise to provide greater rates of seroprotection but has not been studied in HIV
- The ACIP has recently expanded the age range for administration of the HPV vaccine with recommendations for shared decision making in adults aged 27-45
Question-and-Answer