GRADE: Use of HepA Vaccines Among Persons Living with HIV Infection

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GRADE Process

- Develop policy questions
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category

Policy Question: Should routine two-dose vaccination vs. no routine vaccination to prevent hepatitis A be given to adult HIV-positive persons regardless of another indication for vaccination?

Population	Adult HIV-positive persons regardless of another indication for vaccination
Intervention	Routine two-dose hepatitis A vaccination
Comparison	No routine two-dose hepatitis A vaccination
Outcomes of interest	▪ Hepatitis A Infection ▪ Mild Adverse Events ▪ Serious Adverse Events

Outcome Measures Included in Evidence Profile

OUTCOME	IMPORTANCE
Benefits	
(1) Hepatitis A infection	Critical
Harms	
(2) Mild adverse events (any)	Important
(3) Serious adverse events (any)	Critical

Evidence Retrieval

- Systematic review of data on Hepatitis A vaccine and PWHIV[1] including a search of Medline, EMBASE, CINAHL, Cochrane Library, and ClinicalTrials.gov through January 17, 2019

- Search terms included: (((Hepatitis OR HAV OR hepatovirus) AND vaccin*) OR HepA OR Vaqta OR avaxim OR epaxal OR havpur OR Havrix OR nothav) AND (HIV OR human immunodeficiency)

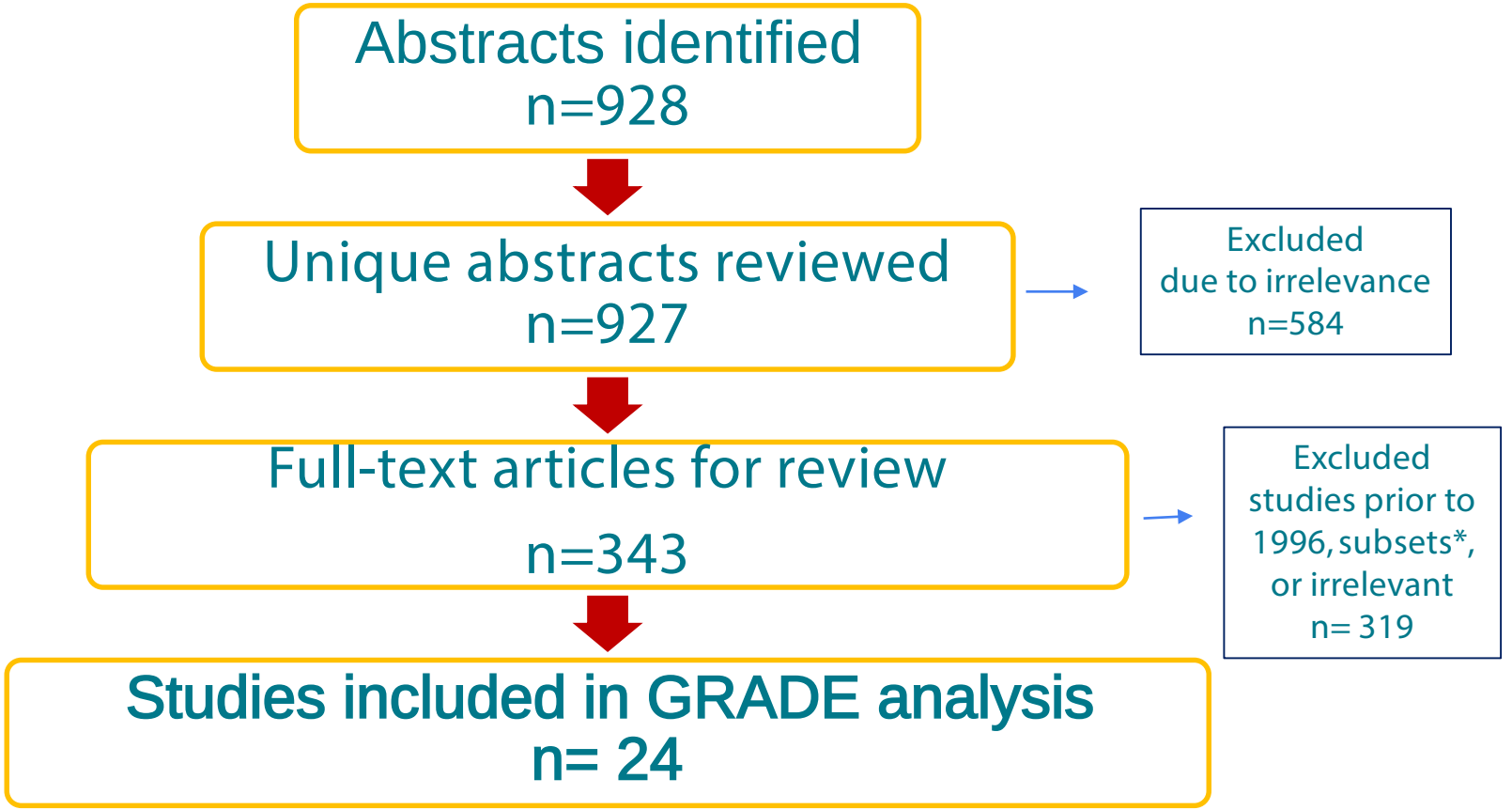
- No language restrictions on initial searches and included articles from any country

[1] PWHIV: Persons Living with HIV

Evidence Retrieval

- ***Exclusion criteria***
  - Articles focused solely on children or articles that did not provide information on ages of included individuals
  - Articles that did not include data on Havrix or Vaqta (the two single antigen hepatitis A (HepA) vaccines currently licensed in the United States)
  - Articles that did not provide new data, only included safety data (not in PWHIV), discussed vaccine introduction, made recommendations or proposed guidelines
  - Articles that could not be obtained in full-text or in English
  - Articles on animals other than humans
  - Clinical trials with no results available

Evidence retrieval



* Articles excluded due to overlap with populations in another included study

Study Design

Abbreviation	Study Design
RCT	Randomized Controlled Trial
Obs	Observational Study

Reference Values

- **Hepatitis A vaccine correlate of protection**
  - 20 mIU/mL (typically varies from 10-33 mIU/mL in the hepatitis A literature)

- **Monovalent hepatitis A vaccines**
  - Vaqta, dosage for ≥19 years: 50 U
  - Havrix, dosage for ≥19 years: 1,440 ELU

- **CD4 cell count**
  - Normal range: 500 - 1,500 cells/mm^3
  - Severely immunocompromised: <200 cells/mm^3

- **HIV Viral load**
  - Undetectable: HIV RNA <20 to 75 copies/mL, depending on the assay used

GRADE of Evidence for Hepatitis A Vaccination in Persons Living with HIV: Benefits

Outcome #1: Hepatitis A Infection Characteristics of included studies

Study	Type	Site	Population N = total	Age	Intervention	Comparison	CD4 Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity*	Main Outcomes #1
Kemper, 2003	RCT	USA	N = 133	mean: 38 years	Havrix, 2 doses, 6 months apart	Placebo, 2 doses, 6 months apart	mean, cells/mm^3: - 376, vaccine - 327, placebo (P, not significant)	mean, $\log_{10}$ copies/mL: - 3.2, vaccine - 3.39, placebo	Month 9: - 68%, CD4 ≥200 cells/mm^3 - 9%, CD4 <200 cells/mm^3 (P = 0.004)	Protective antibody response to vaccination was significantly associated with CD4 cell counts ≥200 cells/mm^3
Launay, 2008	RCT	France	N = 99	mean: 38.8 years	Havrix, 2 doses, 24 weeks apart	Havrix, 3 doses at weeks 0, 4, 24	median, cells/mm^3: 355	median, copies/mL (IQR): <50 (<50–1300)	Week 28, ITT**: - 69.4%, 2-dose group - 82.6%, 3-dose group (P = 0.13)	GMT‡, mIU/mL: 138.2, 2-dose vs. 323.5, 3-dose group at 28 weeks
Wallace, 2004	RCT	USA	N = 180 (90 HIV+)	mean: 32.6 years	Vaqta, 2 doses, week 0 and week 24	Placebo	mean, cells/mm^3: - 457.5, Vaqta - 493.6, placebo	mean, copies/mL: - 0.33 x 10^5, Vaqta - 0.16 x 10^5, placebo	Week 28: 94% among HIV-infected subjects - 87%, CD4 <300 cells/mm^3 - 100%, CD4 ≥300 cells/mm^3	GMT‡, mIU/mL: 517 subjects with CD4 <300 cells/mm^3; 1959, subjects with ≥300 cells/mm^3

*Seroconversion thresholds: Kemper, ≥33 mIU/mL; Launay, ≥20 mIU/mL; Wallace, ≥10 mIU/mL
** ITT: Intention to treat analysis
‡GMT: geometric mean titer

Outcome #1: Hepatitis A Infection Characteristics of included studies

Study	Type	Site	Population N = total	Age, years	Intervention	Comparison	CD4 Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity*	Main Outcomes #1
Armstrong, 2010	Obs	USA	N = 451	mean: 40	HepA (standard dose) or HepB (standard dose) or Twinrix		- 64%, CD4 >400 cells/mm^3 - 36%, CD4 ≤400 cells/mm^3		HepA: - 60%, overall - 62.5%, CD4>400 - 55.56%, CD4≤400	Immune development to HepA increased as CD4 counts increased
Cheng, 2017	Obs	Taiwan	N = 365	mean: 30	Havrix, 2 doses at 0, 6 months; Havrix, 3 doses 0, 1, 6 months		mean: 485 cells/mm^3		primary responders: - 87.3% (2 dose) - 88.9% (3 dose)	GMCs‡ of anti-HAV immunoglobulin G (IgG): significantly higher for 3-dose versus 2-dose
Crum-Cianflone, 2011	Obs	USA	N = 130	median: 35	Vaqta or Havrix, 2 doses, 6–18 months apart	Controls: HIV-negative, VAQTA, 2 doses	median: 461 cells/mm^3	Plasma HIV RNA level, <1000 copies/mL: 49%	89% overall - 78%, CD4 <350 cells/mm^3 - 94%, CD4 ≥350 cells/mm^3	- GMCs‡ among HIV+ adults: 154, 111, and 64 mIU/mL at 1, 3, and 6–10 years - Higher GMCs over time among HIV-infected adults were associated with lower $\log_{10}$ HIV RNA levels (P = 0.04)

* Seroconversion defined as anti-HAV antibody concentrations: Cheng, primary responders: ≥20 mIU/mL at month 12; Crum-Cianflone, ≥10 mIU/ mL at 12 (±6) months after 2nd dose

‡ GMC: Geometric mean concentration

Outcome #1: Hepatitis A Infection Characteristics of included studies

Study	Type	Site	Population N = total	Age, years	Intervention	Comparison	CD4 Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity*	Main Outcomes #1
Horster, 2010	Obs	Germany	N = 131	mean: 40	Havrix, 2 doses at months 1 and 6 or Twinrix (720 EU), 3 doses at months 1, 3, 6; plus additional vaccines**		median: 423.0 CD4/µl	median: below limit of detection	63.6%	Seroconversion was 63.6% among those receiving hepatitis A vaccine
Jablonowska, 2014	Obs	Poland	N = 234	mean age, vaccinated: 30.7	Havrix, 2 doses, 6 months apart		median: 450 cells/mm^3		- 79.5%, one month after 2nd dose - 75.5%, 5 years after vaccination	Most HIV-infected adults with high CD4 counts had a durable response up to 5 years post vaccination
Jimenez, 2013	Obs	USA	N = 226	mean: 41.8	At least 1 dose: a) Havrix b) Twinrix (720 EU)		median: 410 cells/mm^3	median: 1287 copies/mL	- 53.5% overall - 54% (Havrix) - 53% (Twinrix)	- Patients with CD4 counts >350 cell/mm^3 (60%) were more likely to respond than those with CD4 counts <200 cell/mm^3 (35%) (P = 0.0498). - Responders were also more likely to be virologically suppressed (48% versus 32%; P = 0.0024).

* Seroconversion defined as anti-HAV antibody concentrations: Horster, ≥10 mIU/ mL; Jablonowska, , ≥ 20 mIU/ml

** Additional vaccines administered: trivalent influenza split-vaccine (Influsplit) , pneumococcal vaccine (Pneumovax 23), hepatitis B (Engerix; administered at months 1, 3, if Havrix given for hepatitis A)

Outcome #1: Hepatitis A Infection Characteristics of included studies

Study	Type	Site	Population N = total	Age,years	Intervention	Comparison	CD4 Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity*	Main Outcomes #1
Kourkounti, 2012	Obs	Greece	N = 351	median: 40 (range 34-45)	Havrix or Vaqta, 2 doses, 6–12 months apart		median: 564 cells/mm^3	60% had <50 copies/mL at or prior to dose 1 HAV	1 month after the 2nd dose: 74.4% GMTs: 315, 203, 153 and 126 mIU/ml at months 1, 6, 12, and 18	- A higher response rate and higher GMTs were observed in patients with CD4 counts >= 500 cells/mm3 (76.6%) than in patients with CD4 counts 200-499 cells/mm3. - Protective antibody response to vaccination was associated with higher baseline median CD4 count at vaccination.
Kourkounti, 2013	Obs	Greece	N = 113	median: 40	Havrix or Vaqta, 2 doses, 6–12 months apart		median, cells/mm^3: 570	median, copies/mL: <50	After the second dose: 77.0%	GMT‡: HAART patients, 237 mIU/mL [95% CI, 201–321mIU/mL]; no HAART, 158 mIU/mL [95% CI, 130–221 mIU/mL]), p=0.068
Kourkounti, 2014	Obs	Greece	N = 897	mean, vaccinated group: 40.2	Havrix or Vaqta, 2 doses, 6-12 months apart				response rate: 76%	GMT‡: 305 mIU/ml (95% CI 255-361 mIU/ml)
Lin, 2018	Obs	Taiwan	N = 1533	median, vaccinated group: 35	At least 1 dose of HAV vaccine		median, cells/lL: 550		Weeks 28-36: 63.8% (ITT) and 93.7% (PPA)	Vaccine effectiveness: 96.3%

*Seroconversion defined as anti-HAV antibody concentrations: Kourkounti, 2012, ≥20 mIU/ml; Kourkounti, 2013, ≥20 mIU/ml; Kourkounti, 2014, ≥20 mIU/ml

‡ GMT: geometric mean titer

Outcome #1: Hepatitis A Infection Characteristics of included studies

Study	Type	Site	Population N = total	Age, years	Intervention	Comparison	CD4 Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity*	Main Outcomes #1
Mena, 2013	Obs	Spain	N = 499	median: 36.3	(a) Havrix, 1 dose (b) Havrix, 2 doses, 6 months apart (c) Twinrix (720 EIU), 3 doses at 0,7,14–21 days		median, cells/mm3: - 531, standard schedule - 543, rapidly accelerated	median, log_{10} copies/ml: 2.3	Overall rate: 73.4% (a) 60.0% (b) 80.7% (c) 70.7%	- Protective antibody response to vaccination was associated with a higher CD4/CD8 ratio - Higher response was associated with reception of 2 doses of standard schedule (in comparison with those receiving only one of those of the same schedule)
Overton, 2007	Obs	USA	N = 906	mean, vaccinated group: 38.1	Havrix, at least 1 dose		mean, cells/mm^3: 447		49.6% overall	Protective antibody response to vaccination with HIV viral RNA load <1000 copies/ml
Tsachouridou, 2017	Obs	Greece	N = 1210	mean: 34.51	Havrix, 2 doses at 0, 6-12 months; Engerix, 3 doses at 0,4,24 weeks; Pneumovax 23		mean: 2.70 log_{10}	mean, log_{10} copies/ml: 4.18	80.7% seroconversion within 3 months of HepA series completion	Seroprotection not affected by nadir and current CD4 cell count and plasma viral load

*Seroconversion defined as anti-HAV antibody concentrations: Mena, ≥20 mIU/mL; Tsachouriou, ≥20 mIU/mL

Outcome #1: Hepatitis A Infection Characteristics of included studies

Study	Type	Site	Population N = total	Age, years	Intervention	Comparison	CD4 Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity*	Main Outcomes #1
Tseng, 2013	Obs	Taiwan	N = 582 (365 HIV+)	age range: 18-40	(a) Havrix, 2 doses at 6 months apart (b) Havrix, 3 doses at 0,1 and 6 months	(c) Havrix, 2 doses at 6 months apart (HIV- group)	Mean, cells/mm^3: (a) 538 (b) 452	(a) 2.5 log_{10} copies/mL (b) 3.0 log_{10} copies/mL	Week 48 (ITT**): (a) 75.7% for 2-dose HIV+ (b) 77.8% for 3-dose HIV+ (c) 88.5% for 2-dose HIV-	GMC‡ at week 48 ($p < 0.01$): (a) 2-dose, 1.94 log_{10} mIU/mL (b) 3-dose, 2.29 log_{10} mIU/mL Protective antibody response associated higher CD4 counts & undetectable plasma HIV RNA load
Weinberg, 2012	Obs	USA	N = 373	mean: - responders: 41.7 - non-responders: 41.6	HepA (unspecified 2 dose vaccine 6 months apart or 3 dose vaccine every 2 months)		mean, cells/µl: - responders: 519 - non-responders: 450	plasma HIV RNA< 400 copies/ml: -responders: 46% -non-responders: 35%	52% in HAV-seronaive	Plasma HIV RNA <400 copies/ml, higher CD4 cells/µl, and baseline antibody titers <20 mIU/ml (HAV seronaive) were significantly associated with an antibody response to the vaccine
Weissman, 2006	Obs	USA	N = 503	mean: - responders, 43.5 - non-responders, 45.0	Havrix, 2 doses, 6–12 months apart		mean, cells/mm^3: - overall: 424 - responder: 508.6 - non-responder: 344.3		After the 2nd dose (mean of 187 days post series completion): 48.5%	Protective antibody response to vaccination was associated with higher CD4 count

*Seroconversion defined as anti-HAV antibody concentrations: Weinberg, ≥20 mIU/mL; Tseng, ≥20 mIU/mL
**ITT: Intention to Treat
‡ GMC: geometric mean concentration

Outcome #1: Hepatitis A Infection Characteristics of included studies

Study	Type	Site	Population N = total	Age, years	Intervention	Comparison	CD4 Count at Vaccination	HIV Viral Load at Vaccination	Immunogenicity	Main Outcomes #1
Rimland, 2005	Obs	USA	N = 659		Havrix, 2 doses				After the 2nd dose: 60.7%	Protective antibody response to vaccination was associated with higher CD4 count, especially if >200 cells/mm3
Valdez, 2003	Obs	USA	N = 38	median: 38	HAART and IL-2 vaccinated with: Havrix + tetanus toxoid + Remune + Engerix	HAART-only vaccinated with: Havrix + tetanus toxoid + Remune + Engerix	median, cells/μL: - HAART/IL-2: 865 - HAART: 445	median, log_{10} copies/mL (IQR): - HAART/IL-2: 1.7 (1.7 - 2.6) - HAART: 1.7 (1.7 - 1.7)	- 88% of HAART-only recipients - 36% of HAART/IL-2 recipients	Seroconversion was 88% among HAART-only and 36% among HAART/IL-2 groups
Lederman, 2003	Obs	USA	N = 643	median: 40	Havrix, 2 doses, weeks 16 and 40 + multiple antigens*		median, cells/mm^3: 226	median copies/mL: ≤500	8 weeks after second dose: 46%	46% of subjects seroconverted after 2 doses of hepatitis A vaccine

* Antigens included Candida ablicans, mumps skin test, and TT US Pharmacopeia fluid; tetanus toxoid vaccine was also administered at unless previously received in past 12 months.

GRADE of Evidence for Hepatitis A vaccination in Persons Living with HIV: Harms

Outcome #2: Mild Adverse Events
Characteristics of included studies

Study	Type	Site	Population N = total	Age, years	Intervention	Comparison	Main Outcomes #2
Kemper, 2003	RCT	USA	N = 133	mean: 38	Havrix, 2 doses, 6 months apart	Placebo, 2 doses, 6 months apart	- Within 4 days of vaccination, 1 subject (1.6%) in each group experienced severe headache; 1 subject (1.6%) in vaccine group experienced severe fatigue. - Minor injection site soreness: 35% of vaccine doses administered versus 8% of placebo doses ($p < 0.01$). - Reported bacterial, viral, or fungal infections post-vaccination similar for patients receiving vaccine or placebo (24% vs. 26%, respectively; $p > 0.20$)
Wallace, 2004	RCT	USA	N = 180 (90 HIV+)	mean: 32.6	Vaqta, 2 doses, week 0 and week 24	Placebo	- Local reaction at injection site in 57% of Vaqta group and 60% of placebo group - Systemic adverse events (predominantly headache and fever)
Tseng, 2013	Obs	Taiwan	N = 582 (365 HIV+)	range: 18-40	Havrix, 2 doses, 6 months apart	Havrix, 3 doses at 0,1 and 6 months	51.6% of all subjects (HIV+ 51.7% vs HIV- 51.6%, p=0.98) experienced mild tenderness at local injection site within 24 hours of vaccination

Outcome #3: Serious Adverse Events Characteristics of included studies

Study	Type	Site	Population N = total	Age	Intervention	Comparison	Main Outcomes #2
Castro, 2009	RCT	Spain	N = 26	mean: 38.71	Havrix, 2 doses, months 4 and 11; plus 6 usually recommended vaccines*	Placebo at same months as Intervention group	- Vaccinations in successfully treated PWHIV were safe, not associated with increased detectable viral load, and not associated developing genotypic resistance mutations. - Vaccinated group: decrease in $CD4^+$ T cells ($p = 0.046$) associated with increases in activated T cells
Horster, 2010	Obs	Germany	N = 131	mean: 40 years	Havrix, 2 doses at months 1 and 6 or Twinrix (720 EU), 3 doses at months 1, 3, 6; plus additional vaccines**		- No adverse reactions after vaccination reported for those receiving hepatitis A vaccination - No statistically significant difference between pre- and post-vaccination CD4 T-cell counts and HIV plasma load was observed
Launay, 2008	RCT	France	N = 99	mean: 38.8	Havrix, 2 doses, 24 weeks apart	Havrix, 3 doses at weeks 0, 4, 24	- There were no serious adverse events associated with the vaccine. - No significant changes in $CD4^+$ T cell counts or plasma HIV-1 RNA levels during 28-week follow-up
Bodsworth, 1997	Obs	Australia	N = 180	mean: - case: 33.2 - control: 36.6	Havrix, 2 doses at 1 or 6 months apart	No vaccine for Controls	No significant differences ($p > 0.2$) between case and control groups after 1 year for: - AIDS progression, 10.1% versus 10.7% - Death, 7.3% versus 7.6% - mean CD4 decline, 125 $x10^6$/l versus 123 $x10^6$/l No adverse outcomes attributable to vaccination
Wallace, 2004	RCT	USA	N = 180 (90 HIV+)	mean: 32.6	Vaqta, 2 doses, week 0 and week 24	Placebo	No adverse effect on either HIV viral load or CD4 cell count found

*Additional vaccines: hepatitis B (Engerix B; months 0, 1, 2, and 6), influenza (2003–2004 WHO recommended vaccine [A=New Caledonia=20=99 (H1N1), A=Moscow=10=99 (H3N2), and B=Hong Kong=330=2001]; month 1), pneumococcal (Pneumo 23; month 2), varicella (Varilrix; months 4 and 6), measles-mumps-rubella (Priorix,; month 8), and tetanus-diphtheria (Ditanrix Adult; month 10).
**Additional vaccines administered: trivalent influenza split-vaccine (Influsplit), pneumococcal vaccine (Pneumovax 23), hepatitis B (Engerix; administered at months 1, 3 and 6 if Havrix given for hepatitis A)

GRADE Summary

Evidence Types

- **High/Evidence Type 1**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate/Evidence Type 2**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low/Evidence Type 3**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low/Evidence Type 4**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Limitations

- Few studies that directly compare standard 2-dose vaccination versus no vaccination in PWHIV
- Limited studies with hepatitis A infection as study endpoint
- Seroconversion thresholds for hepatitis A antibodies and when test after vaccination varied by study

GRADE Summary

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
BENEFIT						
Hepatitis A Infection	RCT (3)	No serious	Serious[1]	No serious	No serious	2
	Observational (19)	No serious	Serious[1]	Serious[2]	No serious	4
HARMS						
Mild Adverse Events	RCT (2)	No serious	No serious	No serious	No serious	1
	Observational (1)	No serious	No serious	No serious	No serious	3
Serious Adverse Events	RCT (3)	No serious	No serious	Serious[3]	Serious[4]	3
	Observational (2)	No serious	No serious	Serious[3]	Serious[5]	4

[1] Inconsistent seroconversion thresholds for hepatitis A antibodies used, including ≥33 mIU/mL, ≥20 mIU/mL, ≥10 mIU/mL.
[2] Few studies compared the intervention to no vaccine in the comparison group.
[3] One study administered multiple vaccines to subjects.
[4] One study has small population (n = 26)
[5] One study has small population (n = 22)

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