Vaccine-preventable diseases and pediatric HIV infection: Advances and Controversies

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HIV-Specific Immunization Recommendations

- Context of national vaccine programs
  - Prevalence of pediatric HIV infection/exposure
  - Recognition & timing/age of HIV infection
  - Burden of vaccine-preventable disease

### Imunizações

|Quadro 17. Imunização em crianças de 0 a 10 anos de idade, expostas/infectadas pelo HIV |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  | 0 meses | 1 mês | 2 meses | 3 meses | 4 meses | 5 meses | 6 meses | 7 meses | 12 meses | 15 meses | 18 meses | 24 meses | 4 a 5 anos |
| BCG (2) | BCG | | | | | | | | | | | |
| Hepatitis B (4) | Hep B | Hep B | | | | | | | | | | |
| DT (5) | DTP | DTP | DTP | DTP | | | | | | | | |
| Hib (6) | Hib | Hib | Hib | Hib | | | | | | | | |
| Polio inativada (3) | IPV | IPV | IPV | IPV | | | | | | | | |
| Rotavírus (2) | RV | RV | RV | RV | | | | | | | | |
| Pneumococo (15) | Pneu7 | Pneu7 | Pneu7 | Pneu7 | Pneu2 | Pneu2 | Pneu23 | Pneu23 | | | | |
| Meningoeco C (10) | MenC | MenC | MenC | INF | INF | MenC | | | | | | |
| Influenza (1) | INF | INF | INF | INF | INF | INF | INF | INF | INF | INF | INF | INF |
| Tário Viral (12) | TV | TV | TV | TV | TV | TV | TV | TV | TV | TV | TV | TV |
| Varicela (13) | VZ | VZ | VZ | VZ | VZ | VZ | VZ | VZ | VZ | VZ | VZ | VZ |
| Hepatitis A (14) | Hepa | Hepa | Hepa | Hepa | Hepa | Hepa | Hepa | Hepa | Hepa | Hepa | Hepa | Hepa |

OBS.: A vacina contra febre amarela é indicada a partir dos 9 meses de idade, de acordo com a situação epidemiológica local e a condição imunológica do paciente, conforme orientação dos Centros de Referência para Imunobiológicos Especiais (CIRE), do Ministério da Saúde.

### FIGURE 1. Recommended immunization schedule for HIV-infected children aged 0-6 years — United States, 2009

For those who fall behind or start late, see the catch-up schedule.
Issues in Immunization of Children with HIV Infection

- Increased risk/morbidity of vaccine-preventable diseases
  - HIV-infected and HIV-exposed uninfected
- Safety concerns of vaccines
  - Effect on HIV status
  - Disease resulting from live vaccines
- Immunogenicity/Efficacy differences
- Factors related to non-response
  - Improving response rates
- Timing of Immunization vs ART
  - Changes over time in ART criteria, age
ADULTS vs CHILDREN

• ADULTS: Vaccines then HIV Infection
  – Normal immune system maturation
  – Childhood immunizations, Natural Exposure
  – Established immunologic memory
  – Then HIV Infection -> Immunosuppression
  – ART and immune restoration

• CHILDREN: HIV Infection before Vaccines
  – Perturbed immune system (to varying degree)
  – Before vaccines & natural exposure
  – Immunosuppression
  – ART
  – Vaccines before and after (repeat or neo-Ag)
  – Memory?
Increased risk/morbidity of vaccine-preventable diseases with HIV infection

- Invasive bacterial infection
  - Pneumococcal, *H. influenzae* b, Meningococcal
- Tuberculosis
- Measles
- Zoster
- Hepatitis B
- HIV-exposed uninfected children also at increased risk of bacterial infections, TB, measles, hepatitis B
Lower measles antibody among HIV-exposed infants

Geometric mean antibody concentrations to measles virus, by HIV-1 infection or exposure status of the infant and age. Vertical bars indicate 95% CIs. Upper limits 1500 mIU/mL are not shown. Scott, Moss et al. CID 2007; 45:1417–24

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SAFETY: Effect on HIV Status

• Theoretical concern of augmentation of HIV replication by activation of CD4+ T-lymphocytes → accelerated progression to disease

• ↑ HIV Viral Load after immunization observed
  – Tetanus toxoid, injectable influenza, pneumococcal, hepatitis B vaccines
  – Transient

• No evidence of prolonged HIV VL elevation, ↓ CD4+ counts or accelerated HIV disease progression following immunization

• Theoretical concern about brief viremia
  – Pregnancy-MTCT, Sexual Transmission, Resistance
Safety Concerns: 23-Valent Pneumococcal Polysaccharide Vaccine

- Increased pneumonia events in HIV+ PPV recipients
  - Ugandan adults, No ART
  - Randomized, double-blind, placebo-controlled
  - More all-cause pneumonia in vaccine arm \[HR 1.89 (1.1–3.2)\]
  - No sig. difference in mortality, overall pneumococcal events, or first invasive events

- 6-year follow-up
  - Persistent excess of all-cause pneumonia in vaccine recipients \[HR 1.6 (1.0–2.4)\]
  - **But** trend for survival advantage in vaccine recipients \[HR 0.84 (CI 0.7–1.0)\]

- Uncertain significance; Not reported in children

### Safety concerns: SERIOUS ADVERSE EVENTS REPORTED FOR LIVE, ATTENUATED VACCINES IN HIV-INFECTED CHILDREN AND ADULTS

<table>
<thead>
<tr>
<th>Vaccine (# Cases)</th>
<th>Age</th>
<th>Country / Year</th>
<th>CD4</th>
<th>ART</th>
<th>Clinical Manifestations</th>
<th>Outcome</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Polio (2)</td>
<td>4.5y</td>
<td>Zimbabwe 1996</td>
<td>733</td>
<td>No</td>
<td>Flaccid paralysis.. No vaccPV</td>
<td>Permanent paralysis</td>
<td>Lancet 1994, BMJ 1999</td>
</tr>
<tr>
<td></td>
<td>26m</td>
<td>Romania 1994</td>
<td>?</td>
<td>?</td>
<td>Flaccid paralysis. Vaccine PV2.</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Measles (1)</td>
<td>21y</td>
<td>USA 1993</td>
<td>Very low</td>
<td>No</td>
<td>Giant-cell pneumonitis 1 yr after MMR. Measles vacc virus - lung.</td>
<td>Death 5 mos after onset.</td>
<td>MMWR 1996</td>
</tr>
<tr>
<td>Varicella (1)</td>
<td>13m</td>
<td>8</td>
<td>No</td>
<td>Varicella pneumonitis 10wks after vaccine. Vaccine VZV PCR positive from BAL and lung biopsy.</td>
<td>Recovered</td>
<td>JAMA. 2000</td>
<td></td>
</tr>
<tr>
<td>Yellow Fever (1)</td>
<td>53 yo</td>
<td>Thailand 2002</td>
<td>Very low</td>
<td>No</td>
<td>Rapidly progressive myelomeningoencephalitis</td>
<td>Death</td>
<td>J Med Assoc Thai 2002</td>
</tr>
<tr>
<td>BCG</td>
<td>Many reports, of varying severity. Contraindicated i(WHO) n HIV infection since 2007</td>
<td></td>
<td></td>
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Zero (0) reported cases for: Rotavirus, Mumps, Rubella, LAIV
BCG: Problem of timing

• Given at birth in many countries
  – Improves uptake in national programs
  – HIV status for HIV-exposed infants not known
  – HIV exposure status often not known

• ~75% protection against miliary/meningeal TB in HIV-uninfected children
  – TB: major morbidity & mortality in HIV+ children
  – HIV-exposed infants at higher risk of TB exposure during infancy
BCG: Risk without Benefit?


• Efficacy not proven in HIV+ children

• Adverse events in HIV-infected infants
  – 1:20 BCG adenitis
  – ~1:100 disseminated BCG (75% mortality)
  – Most common cause of pediatric IRIS
  – ↓ AEs (including IRIS) with early ART
  – Contraindicated in HIV infection (WHO 2007)
BCG: Other approaches for HIV-exposed infants

- Selective deferral of BCG until 10-14 wks
  - (+) Time of EPI visit
  - (+) After 4-6 week HIV PCR result available
  - (-) Loss to follow-up by 10-14 weeks
  - (-) Ongoing HIV infection risk (breastfeeding)
  - (-) Early TB exposure

- INH prophylaxis to infant
  - Only if known TB exposure?

- Would BCG protect better with early ART?

- New TB vaccine options needed!
  - With vs instead of BCG? For HIV only vs. for all?
  - Administering IL-7 & IL-15 with BCG in mice produced improved CD4 and CD8 T cell memory response Singh 2010
Issues in Immunization of Children with HIV Infection

• Increased risk/morbidity of vaccine-preventable diseases
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• Safety concerns of vaccines
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Vaccine Immunogenicity
Moss 2003

- Pre HAART era
  - Lower response rates
  - Lower GMT
  - Faster antibody decay
- D/T/P, HBV, PCV, PS23, Hib, Measles
- Factors associated with poorer response
  - CD4, VL, Age, HIV Stage
  - *Not consistent* across studies, even of same vaccine
After measles vaccine at 9 mos old, **comparable immunogenicity** for HIV-infected (bold solid) vs HIV-exposed uninfected (dotted) or HIV-unexposed (light solid), but **significantly faster loss of protective antibody**. Infants **not** on ART. *Moss JID 2007*
Quality of Serologic Response

• OPA: opsonophagocytic killing assay
  – Functional assay

• PCV9 series: HIV+ vs HIVneg. PreART Madhi PIDJ 2005
  – Quant Ab similar
  – Lower OPA titers in HIV+ (3/3 ST studied)

• PCV7 series to infants randomized to early vs delayed ART (CHER) at 6-12wks (Madhi JID 2010)
  – Quant Ab similar (though 6B and 14 actually lower in early ART)
  – Lower OPA titers in delayed ART – all ST

• Quantitative immunogenic responses alone may underestimate ongoing risk of vaccine-preventable disease in HIV-infected children
Immunogenicity: HAART before Vaccine

- Meningococcal vaccine naïve youth Siberry 2010
  - Lower response to MCV4 than HIV-uninfected
- Hepatitis A vaccine naïve children Weinberg 2006
  - High seroconversion but low GMT after HAART
  - *P_47:high seroconversion, 34% low GMT (Thai)
- Rubella vaccine response Lima PIDJ2004
  - Rubella response ~ HIV-neg only if CD4≥25%
- HPVV in 9-12 yo HIV+ v HIV- Weinberg CROI 2008
  - HIV+: Lower GMT for 11,16 but same for 6,18
- Pneumococcal conjugate vaccine Abzug 2006
  - CD4≥15%,2-18y. Results ~ healthy child studies
MMR After HAART

Lima PIDJ 2004 (Brazil)

- HIV-1-infected (15- HIV), HIV-exposed uninfected children (20 - SR) and HIV-unexposed (18 - CON) children
- PI-based HAART from infancy (median 4 months)
- MMR at 15 months
- Overall response to Rubella lower for HIV
- Risk Factors: VL and CD4<25%
- CD4≥25% ~ HIV-uninfected

Vaccine response after HAART similar to HIV-uninfected, if HAART effective (associated with good CD4%).
Timing of HAVV after HAART
Rigaud 2008

- HIV+ children with CD4<15%
- Brisk VL response to HAART
- HAVV <4 wks vs 6 mos after HAART
- Titers low compared to healthy children studies
- Titer higher for Delayed vaccines (p=0.008) than early vaccinees
- Seroconversion in 88% of delayed vaccinees vs 60% of early vaccinees (p=0.07)
- No CMI response

Importance of duration of HAART

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Pneumococcal Vaccines: Conjugate Vaccine (PCV) then Polysaccharide Vaccine (PPSV)

- PCV7/PCV7/PPSV23 series in HIV+ children 2-18 yrs old on HAART (N~250)
  - Most received PS23 in the past. No prior PCV7.
  - VL<30K; CD4≥15% (>90% subjects)

- PCV7 at entry and 8 weeks; PS23 at 16 weeks

- ↑ GMC for all PCV7 ST after each PCV dose

- ↑ GMC for ST1, 14, 19F after PS23 (wk 24 titer)

- ↓ GMC at Wk 48 but high rates of “protective” Ab

- Stable->Wk 96

Abzug et al. Pediatr Infect Dis J 2006;25:920
PACTG 1024: PCV then PPSV

• Independent response predictors
  • Entry GMC, CD4%, lower VL, HAART duration, Age<7 yrs old
  • Entry CD4% more important than nadir CD4%
  • Previous PS23 not significant

• Conclusions: Functional immune reconstitution
  • Immunogenic response similar to HIV-uninfected
  • No hyper- or hyporesponse if prestudy PPSV23
HAART Before Vaccine

- Response rates more similar to those in HIV uninfected
- Early, Effective, Extended (time) HAART produces best outcomes
HAART after Vaccine: Does Immunity Reappear?

• Routine immunizations in infancy and early childhood
• Variable degree of immunosuppression
• HAART initiated
• Assessment of immunity
  – Absent: Primary failure, Waning, Lack of memory
• Most common scenario:
  – Includes children diagnosed after infancy and children diagnosed before HAART era
HAART Does Not Reliably “Restore” Immunity to Previous Immunizations

• Measles vaccine in infancy (Thailand; Kenya)
  – ≥5yo, ↑CD4 on HAART. 36% immune. Aupribul 2006
  – Median 4yo, CD4 6%, starting HAART. 33% immune at entry; 42% after 6mos Farquhar2009

• HBV series in infancy/early childhood Abzug 2009
  – 2-19 yr old, stable HAART. Only 24% SAb positive

• Tetanus series in infancy
  – 2-24 yo, CD4<15%, starting HAART. Low TT at entry; No ↑ after 6 mos HAART Rigaud 2008
  – Median 4yo, CD4 6%, starting HAART. 78% immune at entry; 59% after 6mos Farquhar2009 (Kenya)
Vaccine -> HAART -> Vaccine

• Booster dose vs. Repeat series
• Memory response
  – Suggested by Pre-booster immunity, rapid rise in titer, and/or robust rise in titer
• Explanations for no memory response
  – Memory not established with initial series, or
  – Memory lost due to interval immunosuppression
• If no memory response, how likely would repeating series be effective?
Recall Tetanus Toxoid Response

- 2-24yo, CD4<15%, start/new HAART with 2-wk virologic response
- 3-dose Tetanus-containing vaccine (UTD for tetanus at entry):
  - **EARLY** (Group 1: 8, 16, 24 wks) or
  - **DELAYED** (Group 2: 32, 40, 48 wks)
- Single TT vaccine dose – only modest increase in TT Ab - **Minimal memory**
- Primary 3-dose series produced good responses – whether **Early** or **Delayed**
- Similar findings for cell-mediated immunity to TT
- **Suggests absence of memory response but good response to “new series”**

Rigaud. JID 2008; 198. P1006
HBV vaccine immunogenicity and memory response in HIV-infected children on stable HAART

- 2-19 yo, Median 4.8 yrs since last HBV vaccine. All with history of full series. Only 24% HBSAb+ at entry
- 8 wks after HBVV #1: 46% +, 37% ≥4-fold
- 1wk (memory) after HBVV#2: 45% +, 29% ≥4-fold

Predictors of Immunogenic and Memory responses
- Higher baseline HBSAb
- Higher CD4% nadir (memory only)
- Higher CD4% at time of study vaccine
- Undetectable HIV Viral Load

Conclusions
- Low rates of protection against HBV after infant series – response to initial vaccine series important
- Low rates of response and memory after HBV booster doses, despite HAART but mitigated by effective HAART

Abzug JID 2009; 200:935–46. P1024, P1061s
HAART Does Not Reverse Memory B Cell Deficiency

Hart 2007

- IgM memory B cells ↓ in HIV infection and not restored by HAART (figure)
- Impaired PS23 responses in HIV with reduced IgM mem B cells
- Switched memory B cell deficiency common in HIV, with or without ART
- Reduced switched memory B cells associated with impaired humoral immune responses to TT despite HAART
Better Preservation of Memory B Cells with Early HAART

Pensieroso 2009

- Memory B cell number and function reduced if HAART begun after 1st year of life, but normal if HAART begun <1 year

- \( P \leq 0.01 \) Higher rates of protective antibody to measles and tetanus if cART started <2 years old (Italy)

Fig. 1. Early initiation of highly-active antiretroviral therapy preserves memory B cells in vertically HIV-1-infected children. Box plot analyses on the memory B cell percentages in controls and patients with different antiretroviral schedule.
But maybe immunized HIV-infected children are protected despite high rates of apparent lack of immunity?
Protective Efficacy (PE)

• *Haemophilus influenzae* type b (Hib) (SAfr)
  
  *(No ART)* PE for Hib disease: 44% HIV+ v 97% HIV-  Madhi 2002

• Pneumococcal conjugate vaccine (PCV) (SAfr)
  
  – *(No ART)* PE for IPD due to vaccine ST: HIV+ v 83% HIV-  Klugman 2003
  
  – *(20% ART)* PCV9 efficacy at 2 & 6 yrs: 65% & 39% for HIV+; 83% % & 78% for HIV-  Madhi 2007

• Rotavirus
  
  – *(No ART)* Study pop ~5% HIV+. Significant ↓ severe diarrhea. No HIV-specific data - SAfrica/Malawi  Madhi 2010

• Measles (Thailand)
  
  – *(>90% ART)* Outbreak in orphanage. Attack rate for HIV+ = HIV-. Higher attack rate if unimmunized.  Aurptbul 2010
Protective Efficacy (PE)

- Benefit from general population immunization
    - However, IPD dropped 84% after HAART introduction in 1996, but did not decrease further after introduction of routine PCV7 in 2000. (Steenhoff 2008)
- Very little data about vaccine efficacy in population of HIV-infected children on HAART
HBV Infection Risk Not Diminished by Vaccine History in HV Infected Adults

- **Lower** risk of HBV infection in HIV+ adults associated with higher CD4 cell count and use of HBV-active HAART, **but NOT with use of HBV vaccine.** Chun CID 2010

- **No overall reduction in HBV risk if immunized,** but SAb matters (Landrum 2010)
  - HIV+ adults: HBV incidence: 2/100 person-yrs with 11 632 p-y FU
  - HBVV (1 or 3 doses) NOT associated with decreased HBV risk.
  - 11% HBV incidence if HBsAb<10 after vaccine vs 5% if Sab≥10 after vaccine (HR 0.51; CI 0.3–1.0)
  - Chronic infection in 35% with Sab<10 vs 0 with Sab≥10 (P=0.02)

- **Contrasts previous data in healthy people suggesting that those with SAb<10 after full series had ↓ risk of HBV.**
HBV Vaccine Response Predicts Progression to AIDS or Death in HIV-Infected Adults
Landrum #625 CROI 2010

• 19 (9%) HBVV responders vs 102 (25%) non-responders developed clinical AIDS or died (unadjusted p<0.001).
• Positive vaccine response associated with 44% reduced risk of clinical AIDS or death (aHR 0.56)
• Similar results for subset off ART and with CD4 ≥ 350 throughout follow-up (aHR 0.50, 95% CI 0.25-1.01)
• Response to vaccines can elucidate immunologic function in HIV and may have broader prognostic value
So what other factors are determining response to vaccine?

And what other strategies could improve immunogenicity and/or establishment of memory?
HLA class II alleles Predict Non-Response to HBVV in HIV-Infected Adolescents
Li Hum Gen 2009

• Association of HLA class II alleles and haplotypes and magnitude of antibody response to HBVV series in REACH youth
  – Mostly behaviorally acquired HIV infection
  – 255 HIV+, 80 HIV- controls

• Independent predictors of lower Ab response
  – HIV+
    – *HLA-DRB1* variants: 03, 0701, 0804

• “T-helper cell-dependent pathways, mediated through HLA class II antigen presentation, critical to effective immune response to vaccine”
Vaccine Response Impaired by High Regulatory T-cell Counts (T-regs)

delMar-delPozoBalado JID 2010

• T-regs modulate immune response
  – Suppress T (CD4, CD8) & B cells, monocytes
  – T-reg depleted mice: ↑ vaccine response

• HBVV×3 to Adults, HBVV naïve, Sab-neg
  – 50% on ART, CD4 389-591, LogVL 1.6-4.1
  – VL, CD4, Demog – NOT assoc HBVV response
  – ↑T-reg count -> ↑Non-response, ↓Ab titer

• Suggests T-reg as important determinant or even target of immune response in HIV infection

• O_15 Expanded Tregs in children with ↑VL (Italy)
Strategies to Improve Vaccine Response

• HAART (early, effective, extended)
• Higher dose vaccine
• Additional vaccine doses
• Alternative Routes
• Adjuvant
• Nutritional intervention
  – Malnutrition
  – No benefit from vitamin A or Zinc in response of HIV+ adults to PPV23 Deloria 2006
Altering Dosing or Route

• MCV4: 2 doses better than 1 (Lujan-Zilbermann CROI2010)
  – Response to ST A / C / W135 / Y after 1 dose (standard) vs 2 doses: 45% v 73%; 33% v 68%; 60% v 74%; 73% v 84%

• HAVV: 3 doses are better than 2 (Weinberg 2006)
  – 47% low Ab after 2 dose series (standard), improved to only 24% low Ab after 3rd dose.
  CD4>20%, On HAART
Altering Dosing or Route

- HBVV: More may be better ATN024
  - HBSAb+ in HIV+ Adolescents: 60% after 20mcg vs 73% after 40 mcg

- HBVV: Intradermal inferior to IM
  - Abs P_17, Bunupurudah et al
  - 1-18yo HIV+ children, CD4 ≥ 15%/200
  - HBVV 2mcg ID vs 10mcg IM (std)
  - HBSAb titer 268 mIU/mL in ID arm vs 595 in IM arm (p<0.001)
CPG 7909 Adjuvanted-HBV Vaccine in HIV-Infected Adults

- CPG 7909 (Coley Pharmaceutical Group/Pfizer)
  - Activates B cells and dendritic cells via TLR 9
  - Promotes Ag-specific Ab secretion
- 38 HAART-treated adults
  - CD4 ≥200, VL <50 cpm, HBsAb <10 mIU/mL
- Randomized: HBV vaccine (40 mcg) ± CPG 7909 @ 0,1,2 mos.
CPG 7909 Adjuvanted-HBV Vaccine in HIV-Infected Adults


- Seroprotection more rapid w/CPG 7909
- GMTs higher w/CPG 7909
- ↑ LPA responses w/CPG 7909 (T cell help)
- Differences in seroprotection out to 60 mos.
  - Low rate of loss of seroprotection w/CPG 7909
- CPG 7909 safe & well tolerated
  - ↑ injection site pain (p=0.09)
  - ↓ CD4 after doses (resolved by 2 wks post-doses)
  - No difference in VL between groups
Adjuvants in HIV-Infected Adults

• CPG 7909 & PCV7 + PPV23  Sogaard 2010
  – ↑ responder rate, ↑ magnitude, more durable
  – Higher reaction rate
    • Mild systemic & injection site w/PCV
    • Mod-severe flu-like sx’s w/PPV
    • No effect on CD4. Small ↑ VL in HAART-naïve.

• MF59-influenza vaccine (oil in water)
  – Minimal benefit. ↑AEs. No CD4, VL effect

• ASO3-2009 H1N1 (GSK)  Bickel 2010
  – Oil-in-water (squalene, tocopherol, polysorb 80)
  – Response rates still < HIV Θ. Safety?

• NO studies of adjuvanted vaccine in HIV+ children
SUMMARY

• Important: Major morbidity/mortality in HIV+ patients from vaccine-preventable diseases
• Safety: No effect on HIV
• Non-live vaccine: Safe
• Live vaccines: Rare reports of adverse events; avoid all in advanced HIV
• Enhancing response- especially initial response
  – HAART is important but may not reverse all deficits
  – HAART is best if …Early, Effective, Extended time
  – Additional or Higher Doses, Boosters, Adjuvants
• With routine HAART from early infancy, immune responses (immunogenicity/memory) may normalize and live-vaccine risks may decrease.
Summary (cont’d)

• Need more data about vaccine efficacy in children on ART
• Routine reimmunization after reconstitution on HAART
  – Routine reimmunization vs Individual assessment
  – Response to new antigen or new series may be more reliable than booster/memory response
• Exploit immunologic evaluations of vaccine response to investigate immunologic function on HAART
• Genetic determinants
• Importance of context of country/regional epidemiology
  – Minimize disrupting effective EPI programs
  – Benefit to HIV-infected populations from herd immunity
  – BCG in areas with high TB and HIV burdens in context of declining HIV perinatal infections
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