Infectious Complications in HIV-Infected Children and Adolescents

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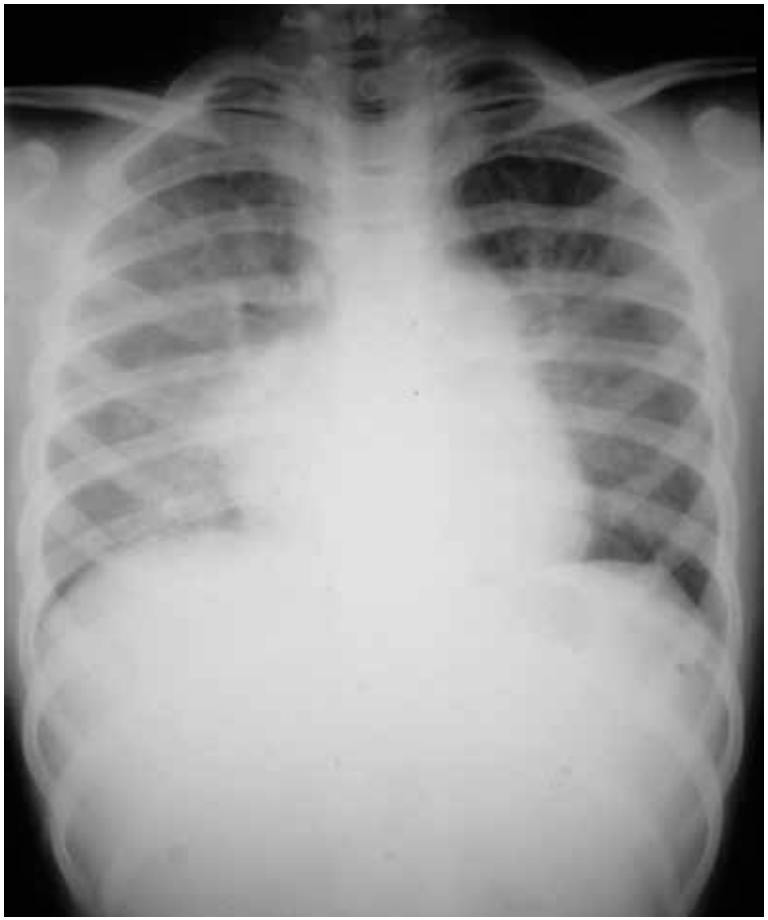
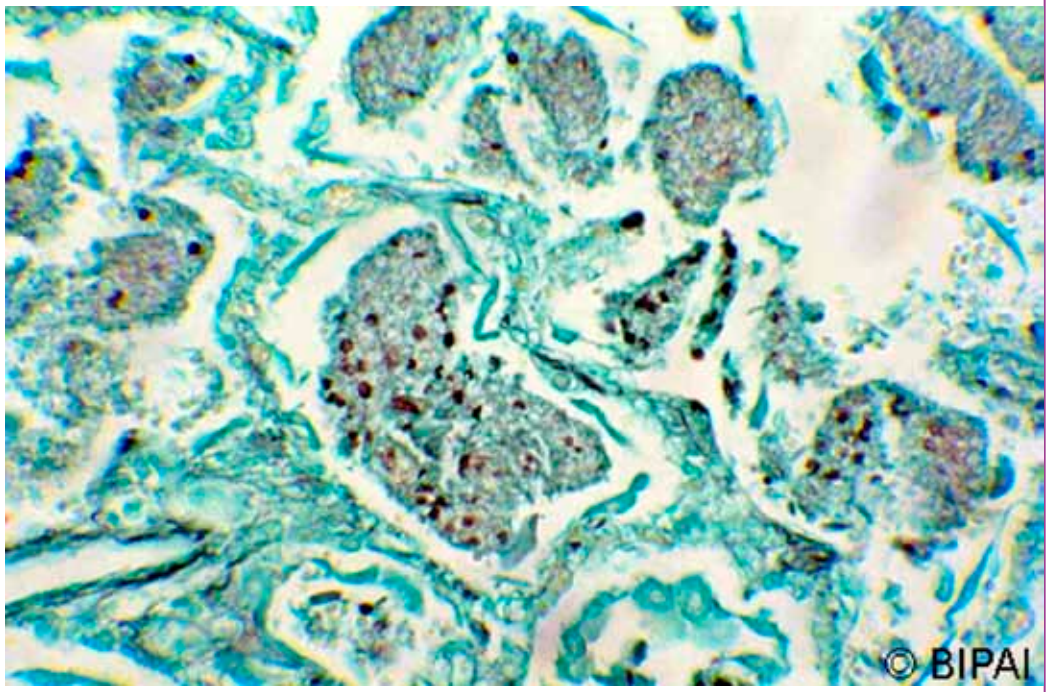
PCP Pneumonia





Pneumocystis jirovecii pneumonia (PCP), an opportunistic infection, heralded the HIV/AIDS epidemic in 1981

Infectious Complications in HIV

- Incidence of targeted infections led to clinical diagnosis of AIDS
  - Bacterial infections, multiple or recurrent
  - Candidiasis (not oral)
  - Endemic mycosis
  - Cryptosporidiosis or isosporiasis, chronic
  - Cytomegalovirus disease or retinitis
  - Chronic herpes simplex
  - MAC
  - Tuberculosis
  - *PCP*
  - Pneumonia, recurrent
  - *Salmonella* septicemia
  - Toxoplasmosis of brain

Infections in HIV-Infected Children – Pre-HAART Era

TABLE 2. Event rates for serious opportunistic infections

OI Diagnosis	No. of Events	Event Rate (Per 100 P-Y)	95% CI
Serious bacterial infections	879	15.1	14.2–16.1
Herpes zoster	199	2.9	2.6–3.3
Disseminated *Mycobacterium avium* complex	126	1.8	1.5–2.1
Pneumocystis carinii pneumonia	92	1.3	1.1–1.6
Candidiasis	87	1.2	1.0–1.5
Cryptosporidiosis	41	0.6	0.4–0.8
Cytomegalovirus-retinitis	33	0.5	0.3–0.6
Tuberculosis	27	0.4	0.3–0.6
Cytomegalovirus-other	16	0.2	0.1–0.4
Fungal	8	0.1	0.05–0.2
Toxoplasmosis	4	0.06	0.02–0.1
Progressive multifocal leukoencephalopathy	4	0.06	0.02–0.1

P-Y, person years; 95% CI, 95% confidence interval.

- Infections were a major cause of morbidity and mortality in pediatric HIV-infected patients prior to HAART
- Among serious bacterial infections, pneumonia and bacteremia most common
- OIs were cause of death in 37% of children in US cohort and 58% in Spanish cohort

Data from 3,331 HIV-infected US children from 13 clinical trials

Dankner, Pediatr Infect Dis J 20:40, 2001; Brady, JAIDS 53:86, 2010; Palladino, Pediatr Infect Dis J 30:495, 2011

Pneumocystis jirovecii Pneumonia (PCP)

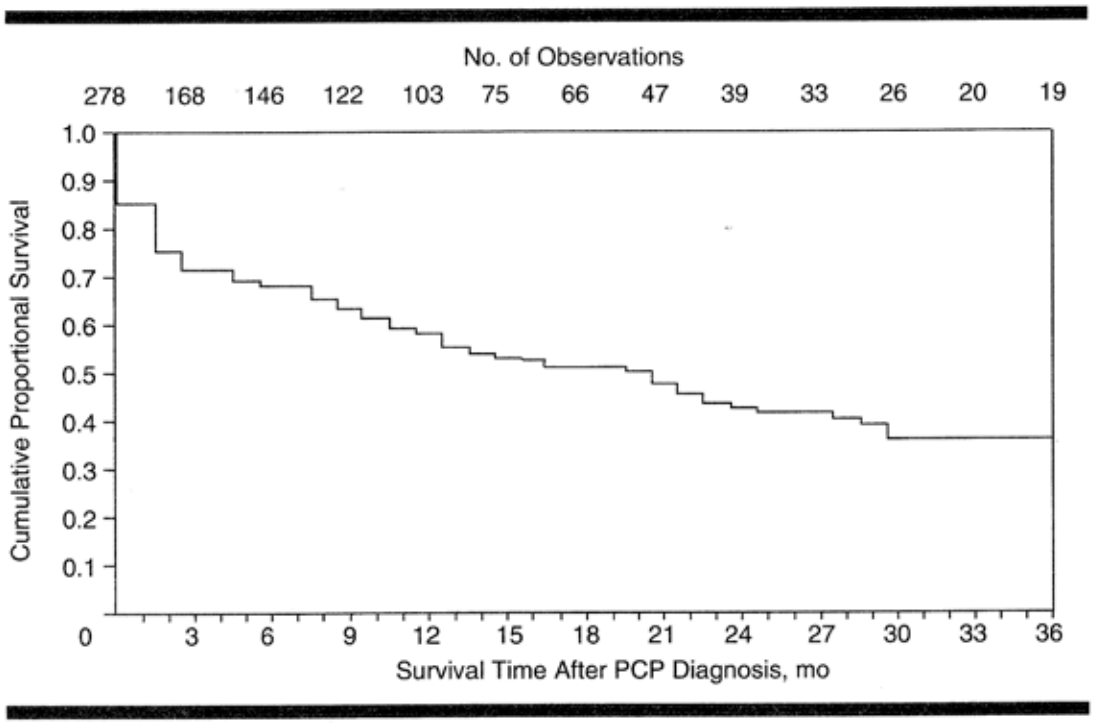
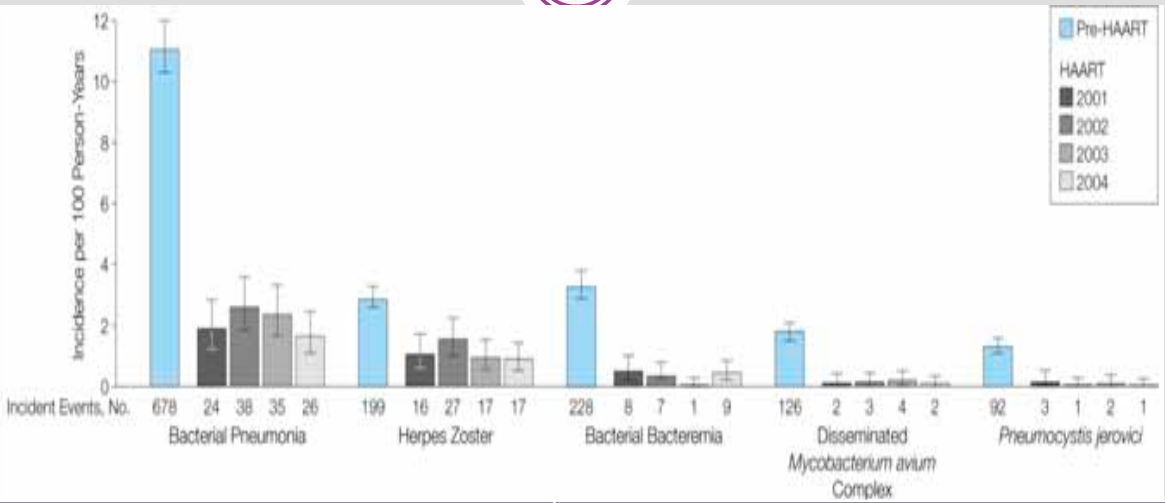


Fig 3.—Cumulative proportion of children surviving following *Pneumocystis carinii* pneumonia (PCP) diagnosis among children for whom follow-up information was available (n=278), who were enrolled in the Pediatric HIV Spectrum of Disease Project, in months. Number of children surviving who have follow-up information available at the beginning of each 3-month interval is indicated at the top of the figure.

- PCP reported in 37% of all early pediatric AIDS cases, 61% in those diagnosed in the first year of life
- Most cases diagnosed between 3 – 6 months of age
- Often led to HIV infection diagnosis
- Median survival after PCP diagnosis was 19 months

Simonds, JAMA 270:470, 1993

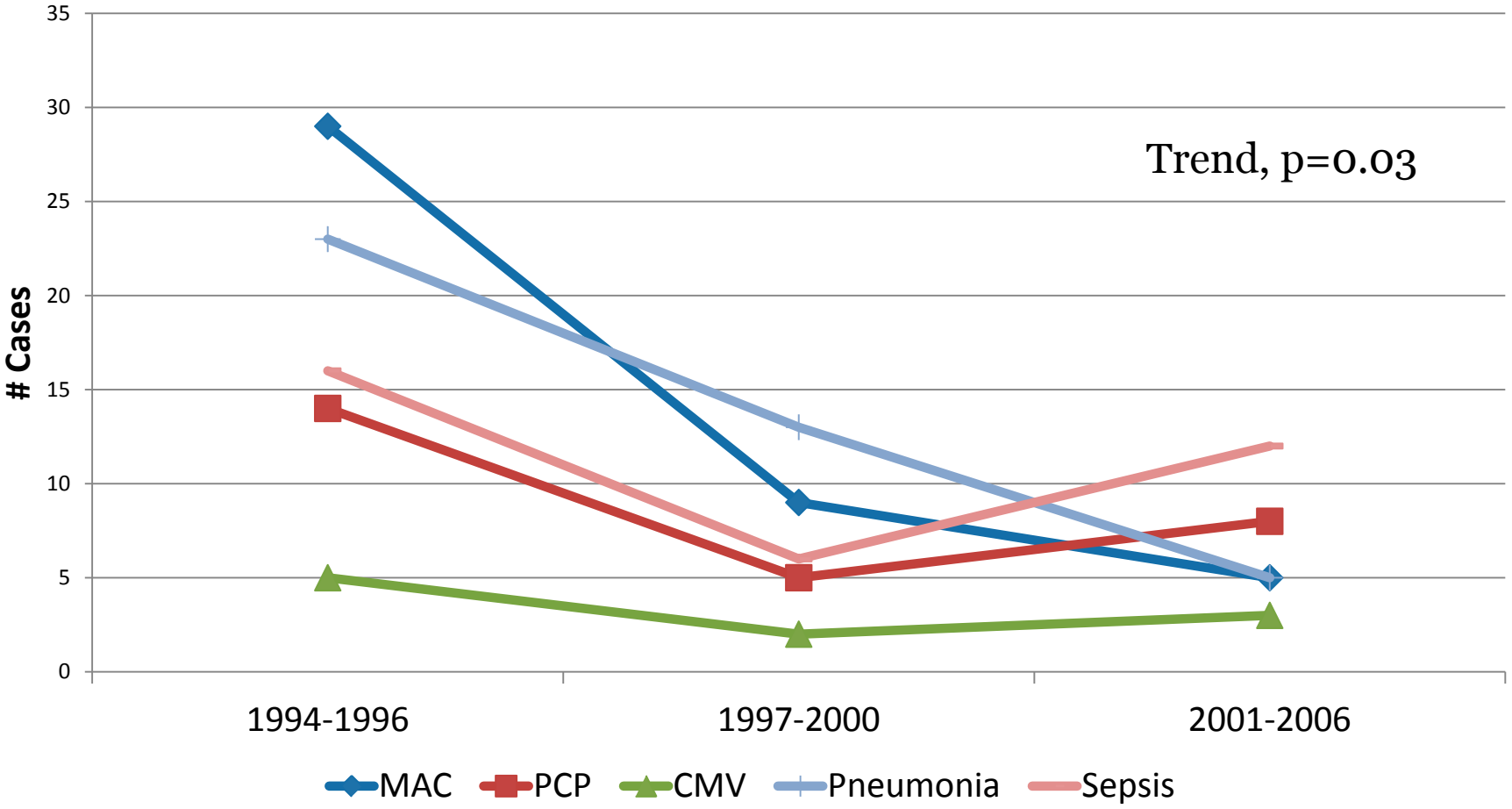
Impact of Antiretroviral Therapy



	Incidence rate per 100 person- yrs	
	Pre-HAART	Post-HAART
Bacterial pneumonia	11.1	2.15
Bacteremia	3.3	0.35
Herpes zoster	2.9	1.11
Disseminated MAC	1.8	0.14
PCP	1.3	0.09

Gona, JAMA 296:292, 2006

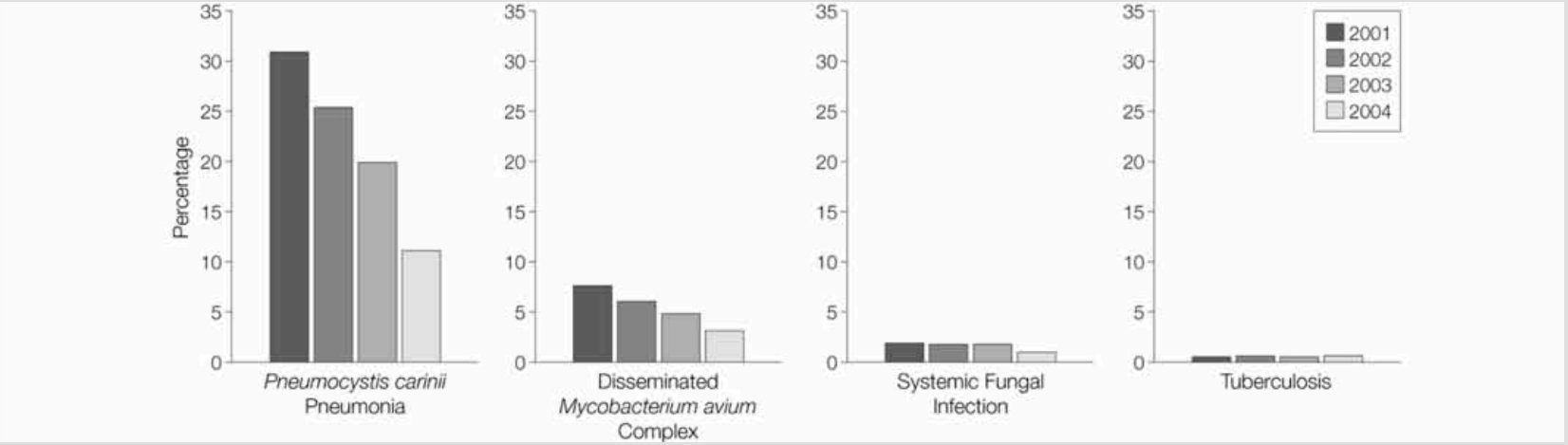
Primary Cause of Death for HIV-Infected Children by Year – PACTG 219C



Brady JAIDS 53:86, 2010

Reasons for Reduction in Incidence?

- Reduced severity of immunosuppression due to widespread use of HAART
- Immunization (*Streptococcus pneumoniae*, varicella zoster)
- Expanded and more aggressive use of prophylaxis



Gona, JAMA 296:292, 2006

PACTG 219 – Infections in the Post-HAART Era

- Most common infections (events /100 person-yrs)
  - Bacterial pneumonia – 2.15
  - Herpes zoster – 1.11
- Other emerging infections of significance
  - Human papilloma virus infection
- Infections not discussed
  - Tuberculosis
  - Hepatitis

Gona, JAMA 296:292, 2006

Bacterial Infections

- Higher risk in HIV-infected compared to HIV-uninfected or exposed
  - May result from reduced amounts of maternal antibody transferred in utero, qualitative B cell deficits, impaired neutrophil response
- Bacteremia, sinusitis and otitis media more common
- Bacteremias with *S. pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* more common than in uninfected
- In the HAART era, pneumonia rates similar to uninfected children

Mofenson Clin Infect Dis 21:1175, 1995; CDC, MMWR 2009;58(No. RR-11

Systematic Review of Pneumonia in HIV-Infected Children

- Review of 15 published studies meeting pre-determined criteria (included clinical and postmortem studies)
- Includes both pre-HAART and HAART eras
- Among bacterial pathogens
  - *S. pneumoniae*
  - *Haemophilus influenzae*
  - *S. aureus*
  - *Salmonella* sp.

Punpanich, Pediatr Infect Dis J 30:e192

Community Acquired Pneumonia (CAP) in US, 2000- 2005

- High rates of HAART (70%) and pneumococcal vaccination (90%)
- Overall rate of CAP 3.3 cases per 100 pt- years
- Peak incidence in 2001 at 5.3 cases/100 pt yrs; nadir in 2005 at 1.7 cases/100 pt yrs
- Decline may be related to aging of the cohorts since younger age was a risk factor for infection
- Viral load > 100,000 copies/mL was a risk factor for development of CAP

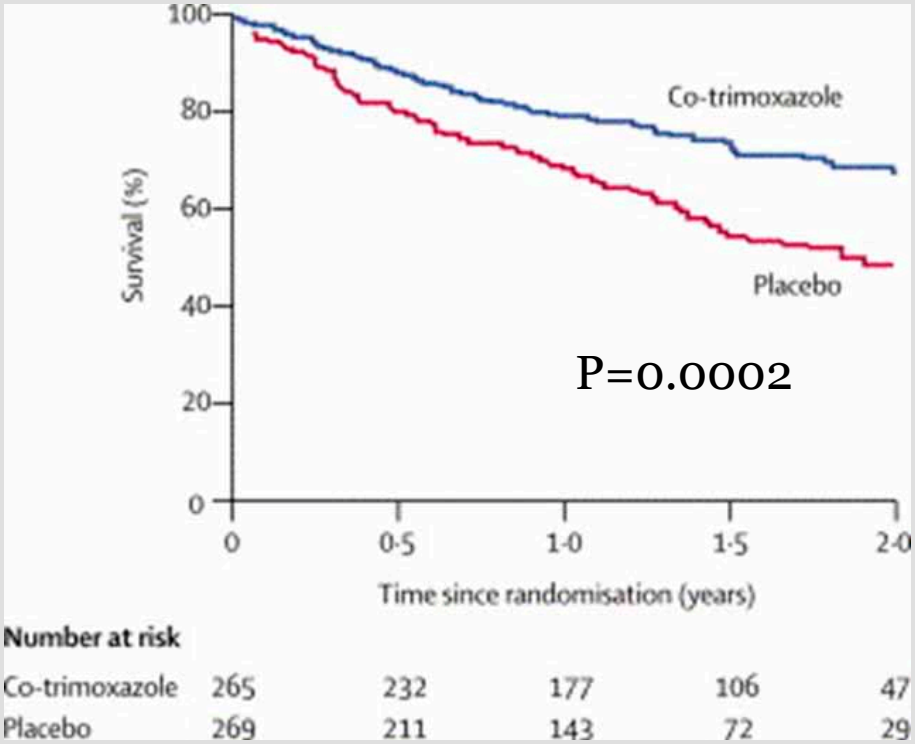
Steenhoff , AIDS 25:715, 2011

Prevention of Infections

- Immunization against *S. pneumoniae* and *H. influenzae*
- In patients with hypogammaglobulinemia (IgG < 400 mg/dL), IVIG can be administered
- Trimethoprim-sulfamethoxazole/cotrimoxazole prophylaxis
  - Effective for PCP prophylaxis
  - Other benefits?

CHAPS Study - Zambia

- Randomized HIV-infected children, age 6 m – 14 yrs, to CTX or placebo
- Median CD4 % was 11%
- No ARV therapy
- 541 children randomized
- Trial stopped early
- Also had fewer hospital days
- Largest impact on lower respiratory tract infection



Mulenga, AIDS 21:77, 2007; Chintu , Lancet 264:1864, 2004

Prevention of Infections

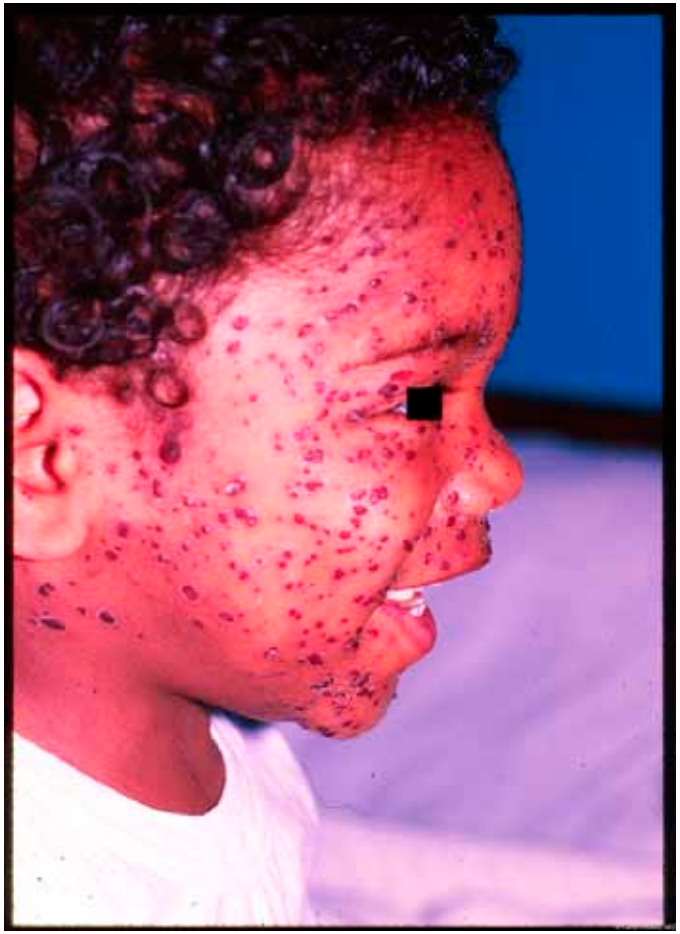
- Immunization against *S. pneumoniae* and *H. influenzae*
- In patients with hypogammaglobulinemia (IgG < 400 mg/dL), IVIG can be administered
- Trimethoprim-sulfamethoxazole/cotrimoxazole prophylaxis
  - Effective for PCP prophylaxis
  - Reduces overall mortality
  - Reduces hospitalizations and documented infections, especially lower respiratory tract infections

Recommendations for CTX Usage

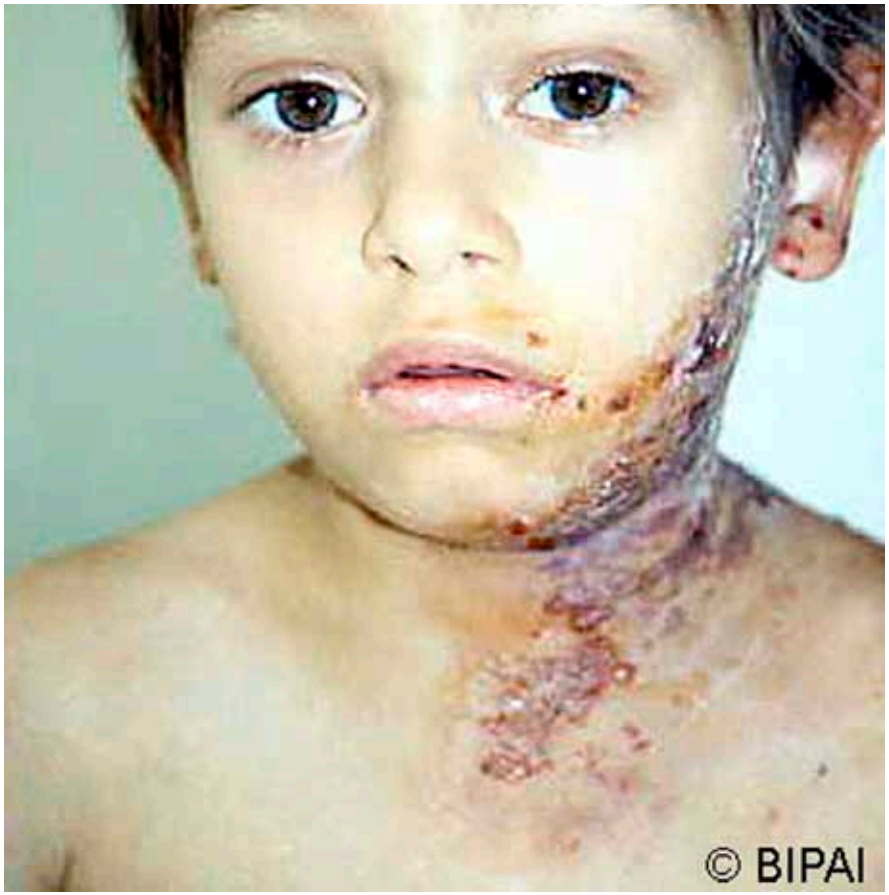
- US, European and WHO recommendations similar
- Between 1- 4 years, US recommends for CD4 <500 or <15%; PENTA recommends for CD4 <500 or 20%

Situation			
Hiv-exposed infants and children[a]	Infants and children confirmed[b] to be living with hiv		
	<1 Year	1–4 Years	≥5 Years
Co-trimoxazole prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection [A-III]	Co-trimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status [A-II][c]	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage OR Any WHO stage and CD4 <25% [A-I]	Follow adult recommendations
Universal option: prophylaxis for all infants and children born to mothers confirmed or suspected of living with HIV. This strategy may be considered in settings with high prevalence of HIV, high infant mortality due to infectious diseases and limited health infrastructure [C-IV].			

Varicella Zoster Virus



Primary varicella infection



Herpes zoster infection

Varicella Zoster Virus Infection

- Prior to HAART, varicella could present as a severe infection
- Up to 14% developed chronic varicella infection with new lesions developing for over 1 month
- Before availability of HAART, 27% of children who developed varicella developed zoster a mean of 1.9 years after varicella
- If CD4 count was < 15% at the time of varicella, 70% developed zoster
- Recurrent episodes of zoster common

Varicella Zoster Virus Infection

- Safety and efficacy of live attenuated varicella vaccine in children with HIV infection studied
- Targeted HIV-infected children, age 1 – 8 years with CD4 ≥ 15%
- Two doses of vaccine administered 3 months apart
- Vaccine was well tolerated
- Two months following vaccine, 60% had detectable antibody and 83% positive LPA responses
- How effective is vaccine in preventing primary varicella and zoster?

Levin, J Pediatr 139:305, 2001; Levin, J Infect Dis 194:247, 2006;

Effectiveness of Varicella Vaccine in HIV Infected Children

- In vaccine era, both unvaccinated and vaccinated were protected
- If vaccinated, no cases developed zoster

Group	No. of cases	Incidence, cases/1000 PYs
	Varicella[a]	
Unvaccinated, prevaccine era	64	103.3
Unvaccinated, vaccine era	19	36.8[b]
Vaccinated[c]	2	6.8
	Zoster	
Unvaccinated, pre-HAART era	7	59.4
Unvaccinated, HAART era	25	40.4
Unvaccinated, receiving HAART	15	43.6
Unvaccinated, receiving HAART and excluding IRIS	12	34.9
Vaccinated	0	0

NOTE. Differences in the incidence of varicella and herpes zoster after vaccination are significantly lower among vaccine recipients than among children with natural infection ($P < .01$; see the main text for details). The effectiveness of varicella vaccine was 82% in preventing varicella and was 100% in preventing herpes zoster. PYs, person-years.

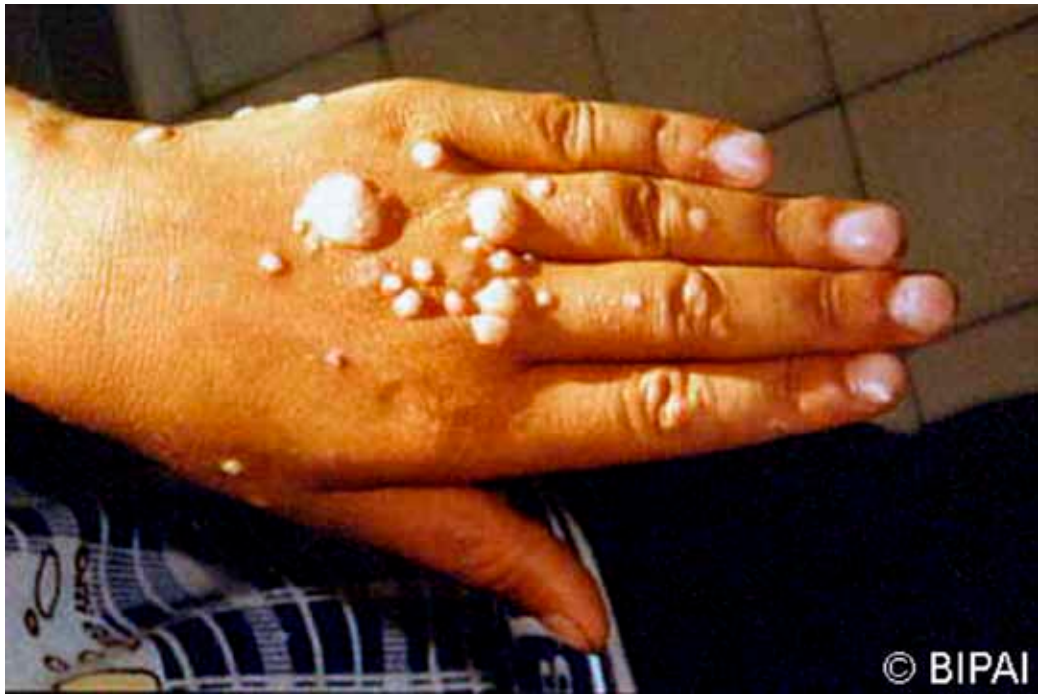
[a] A total of 83 unvaccinated children developed varicella; there were 32 subsequent cases of herpes zoster in this group.

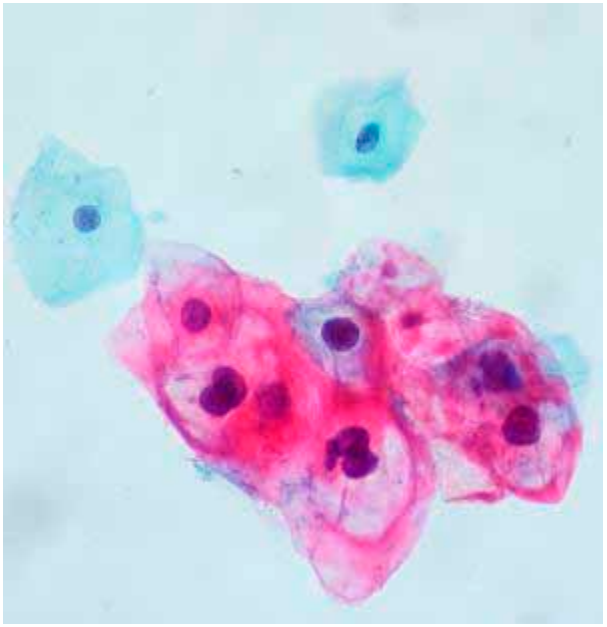
[b] Incidence decreased 63% during the vaccine era, compared with the prevaccine era.

[c] Of 72 vaccinated children, 2 developed breakthrough varicella, and 0 developed herpes zoster.

Son, J Infect Dis 201:1806. 2010

Human Papilloma Virus Infection





Human Papilloma Virus Infection

- Over 100 types of human papilloma viruses (HPV)
- 12 are identified as high risk for development of cervical, vulvovaginal, and anal cancers
- In immunocompetent persons, infections are mostly transitory but infection persists in HIV infected persons
- Among youth with HPV, persistence, but not high grade lesions, is associated with lower CD4 counts

Moscicki J Infect Dis 190:1413, 2004

HPV in HIV-Infected Children and Adolescents

- Among children followed in PACTG 219C, cervical dysplasia occurred at a rate of 5.92 events per 100 person years
- Abnormal PAP tests were more likely among those with history of STI or CD4 < 200
- If sexually active, mode of HIV infection did not influence presence of an abnormal PAP smear

Nachman Arch Pediatr Adolesc Med 163:164, 2009; 25: 27, Setse J Pediati Adolescn Gynecol , 2012

Prevention of HPV in Children with HPV

- Avoid exposure using safer sexual practices
- Immunization
  - P1047 studied 126 HIV-infected children, age 7-11 years
  - CD4 was ≥ 15% and on HAART if CD4 < 25%
  - Safety and tolerability similar to HIV-uninfected
  - Most all groups developed antibodies to all HPV types in the vaccine (6,11, 16, and 18)

Levin, JAIDS 55:197, 2010

Summary

- Availability of HAART has resulted in improved immune status of HIV-infected children
- Improved immune status has resulted in a shift in types of infections away from opportunistic infections associated with severe immunosuppression to other infections
- Bacterial infection, including pneumonia, herpes zoster infections are rising in importance
- HPV infections introduce a new risk because of increased rates of persistent infection and subsequent development of cancer

Recommendations

- HAART to maintain immune competence
- Immunizations for *S. pneumoniae*, *H. influenzae*, varicella zoster, and HPV
- Cotrimoxazole prophylaxis based on locale and immune status
- Surveillance for HPV related cancers with PAP smears in sexually active adolescents