


18th Annual
HIV CONFERENCE
of the Florida/Caribbean AIDS Education and Training Center

May 1-2, 2009
Orlando, FL

Opportunistic Infections in HIV Positive Children

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Disclosure of Financial Relationships

**This speaker has no significant financial
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This slide set has been peer-reviewed to ensure that there are
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Objectives for Presentation

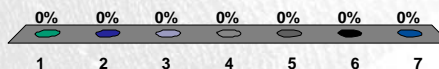
- Recognize differences in opportunistic infections between children and adults infected with HIV
- Understand the management and prevention of specific opportunistic infections in HIV + children
- Know the “ready - available” resources for managing complicated infectious situations in HIV + children

Guidelines for Prevention and Treatment of OIs among HIV-Exposed and HIV-Infected Children <http://AIDSinfo.nih.gov>



Please select your Profession

1. Nurse
2. ARNP
3. Pharmacist
4. Case Manager
5. Physician Assistant
6. Dentist
7. Physician



Estimate of Risk of Opportunistic Infection

- Previous HIV-related illnesses / infections
- Previous classification / stage of disease
- Current CD-4 percentage (%) and total count (immunologic category)
- Vaccination History and / or evidence of serologic “protection” (protective antibody levels)
- Other underlying / concurrent illness

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Immunologic Categories in Children

| Category | <12 months old | 1-5 years of age | 6-12 years of age |
|------------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|
| | % Per mm ³ | % Per mm ³ | % Per mm ³ |
| 1. No Suppression | >= 25% >= 1500 | >= 25% >= 1000 | >=25% >= 500 |
| 2. Moderate Suppression | 15-24% 750-1499 | 15-24% 500-999 | 15-24% 200-499 |
| 3. Severe Suppression | <15 % <750 | <15 % <500 | <15 % <200 |

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Common Infections in Children with “No Suppression”

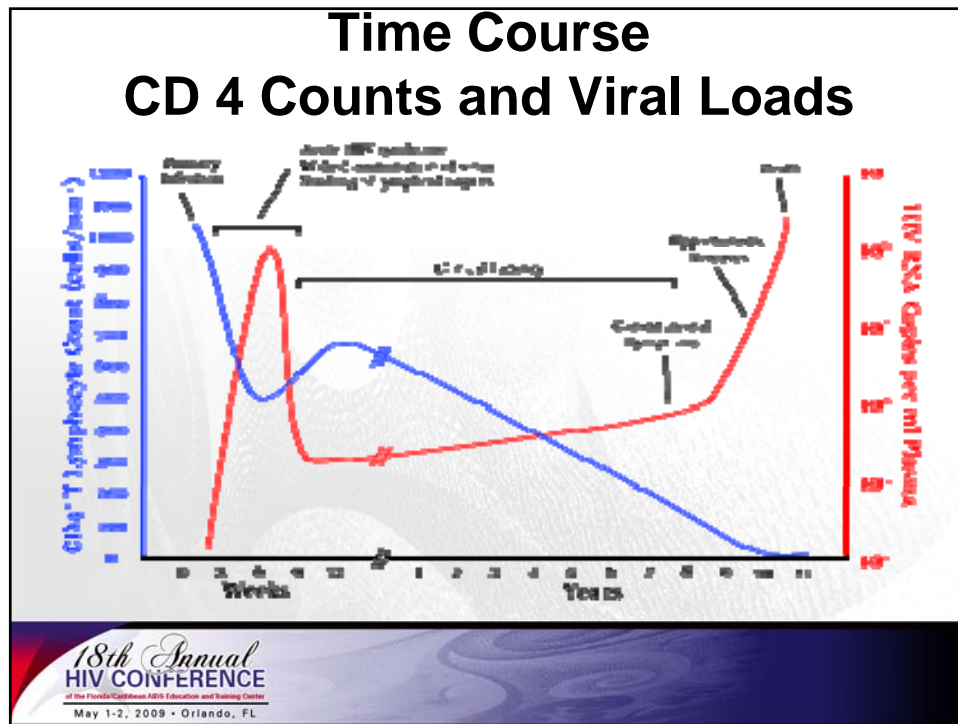
- Thrush
- Primary Herpetic Gingivostomatitis
- Pneumonia – *Streptococcus pneumoniae*
- PCP in infants < 1 year old (*P. jiroveci*)
- Tuberculosis (TB)
- Otitis Media
- Sinusitis
- Bacteremia

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Common Infections in Children with Severe Suppression

- PCP
- Cryptococcus
- Cryptosporidium
- Varicella
- Zoster
- Bacteremia
- Non-tuberculous Mycobacterium (NTM, MAC)
- Toxoplasmosis
- Recurrent Herpes simplex (HSV)
- CMV

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Incidence of Infections in HIV + Children in the pre-HAART Era

- Otitis media – 57 cases/100 pt. years
- URI – 47
- Sinusitis – 15
- Bacterial Pneumonia – 11
- Bacteremia – 8.2
- UTI – 3.7
- Meningitis – 1.1 cases/100 pt. years

Van Dyke RB. Ann NY Acad Sci 1993; Feb



Incidence of Infections in HIV + Children in the pre-HAART Era

- PCP – 6.4 cases per 100 patient-years
- Herpes Zoster – 5.0
- Varicella – 4.7
- MAC – 2.6
- CMV – 2.4
- Cryptosporidiosis – 1.1
- Tuberculosis – 1.0

Van Dyke RB. Ann NY Acad Sci 1993; Feb

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Common AIDS- Defining Illnesses in Children

- PCP 25%
- Recurrent bacterial infections 18%
- Esophageal + tracheobronchial candidiasis 12%
- CMV 8%
- MAC infections 7%
- HSV infections 3%
- Cryptosporidiosis 2%

CDCP HIV-AIDS surveillance report CDCP 1997;9 (No.2):1.

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Decrease in Incidence of OIs in the post-HAART Era

- **Bacterial Pneumonia**
11.1 – **2.2** cases per/100 pt.-years
- **Bacteremia** 3.3 – **0.4**
- **Herpes Zoster** 2.9 – **1.1**
- **Disseminated MAC infection** 1.8 – **0.14**
- **PCP** 1.3 – **0.09** cases / 100 pt.-years
- **Comparing years 1988-98 to 2000-04, PACTG 219 Study**

Guidelines for Prevention & Treatment of OIs among HIV-exposed and HIV-infected Children 6/20/2008

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Special Considerations for HIV Positive Children and OIs

- **Primary infection with the pathogen**
(PCP, HSV, CMV, etc.)
- **Vertical transmission from HIV+ mother**
(Hepatitis C, CMV)
- **Horizontal transmission in households**
(TB, pneumonia, Varicella Zoster Virus)
- **Direct detection of pathogens**
(passively acquired maternal antibody)
- **Pharmacokinetic and pharmacologic issues**

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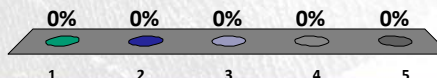
Case # 1

- A 7 yo HIV + girl has cough, abdominal pain, cervical and axillary adenopathy, bilateral rales and a large liver.
- A 10 day course of clarithromycin did not improve her symptoms. Her CD4 count was 291/20%, her hemoglobin was 8.9, but other labs were WNL.
- After another week, her cough improved, she was sweating a lot but had not had fever or weight loss.
- Her adult cousin (who had been in prison) had pulmonary tuberculosis 2-3 years ago [household contact].

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What pulmonary disease does this patient have?

1. PCP
2. Tuberculosis
3. MAI
4. Pneumococcal pneumonia
5. Aspergillosis



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What do you think now?



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Baylor
COM

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TB / HIV Comorbidity U.S., 1993-2004

- TB/HIV case rate decreased from 1.4/100,000 in 1993 to 0.4/100,000 in 2004.
- The highest comorbidity rate is in 25-44 year olds – 19.8% HIV+ of pts. with TB.
- In children 0-4 years old, 78 (5.1%) were HIV + of 1542 children with TB tested for HIV of 6199 children with TB in age group.
- Children 5-14 years old, 59 (4.1%) were HIV + of 1192 tested in the 4344 children with TB in this age group.

Albalak, R. Trends in TB/HIV Arch Int Med 167(22):2443-52, 2007.

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MDR and XDR-TB U.S. 1993-2007

- **MDR – resistance to INH and a rifamycin**
- **XDR – resistance to I, R + other agents**
- **XDR-TB in 83 cases from 1993-2007**
- **XDR-TB 0.07% in 1993 and 0.02% in 2007**
- **XDR-TB was more likely associated with disseminated disease, smear + sputum, prolonged infectious period and mortality**
- **Ages 0-14 years – 61 MDR and 2 XDR-TB**

Shah S. XDR-TB in US, 1993-2007. JAMA 300(18):2153-60, 2008

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HIV Positive Children *Mycobacterium Tuberculosis*

- **Children <4 years old or HIV + are likely to develop active disease once infected.**
- **Pulmonary TB is hard to differentiate from other OIs in the lungs.**
- **Children with HIV and TB are more likely to have atypical findings + extrapulmonary disease.**
- **Look for the adult contact.**
- **TST – cutoff \geq 5mm**

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Suspect MDR-TB in a Child

- Close contact of MDR-TB patient
- Contact with a patient who died of TB
- Child with TB not responding to first-line drugs given via DOT
- The apparent source case that remain smear or culture positive after 2 months of DOT
- Children born in or exposed to residents of countries or regions with high prevalence of MDR-TB

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TB Treatment in HIV positive Children

- Think TB!
- Empiric Treatment with 4 drugs (INH, RIF, PZA, ETM, or STM)
- DOT – daily for 2 months, then BIW or TIW with a “tailored regimen” – based on sensitivity testing
- Duration – 6-9 months of therapy, and > 12 months for extrapulmonary disease – bones, joints, CNS or miliary disease

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TB and ARV Treatment in Children

- ARV naïve – defer ARV treatment if possible, based on CD4 counts and viral load (8 weeks or 9 months)
- ARV experienced – start TB Rx immediately, assess HIV status, review ARV medication options and potential toxicities and interactions
- Do not use Rifampin or rifapentine, rifabutin OK with certain PIs and certain NNRTIs – consult a pediatric HIV expert

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TB Prevention in HIV Positive Children

- Prevent Exposure ??
- TST @ 3 months of age, time of HIV diagnosis and yearly
- Cough Questionnaire
- Chest X-ray
- Prevent Disease Latent TB Infection (LTBI) – treatment with either INH for 9 months or RIF for 6 months
- Recurrence / reactivation rare after LTBI treatment – no chronic therapy recommended
- Primary prophylaxis (with exposure) – INH or RIF
- Secondary prophylaxis is not recommended

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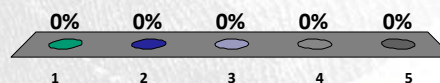
Case # 2

- An 11 month old, HIV + infant is adopted from Ecuador
- Baseline CD4 counts 12%, 562 and viral load of 162,000
- Patient began ART – AZT, 3TC, NVP
- 2 weeks later the BCG site began to swell and ooze purulent material, but the child was afebrile with tender left axillary nodes

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What illness does this patient have?

1. Immune suppression
2. Bacterial Lymphadenitis
3. BCG Lymphadenitis
4. Immune Reconstitution Inflammatory Syndrome
5. 3 + 4



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Immune Reconstitution Inflammatory Syndrome (IRIS)

A



B



Dunkley-Thompson et al. BCG Lymphadenitis and IRIS

West Indian Medical Journal 57(3), June 2008

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- Proposed clinical definition: worsening symptoms of inflammation or infection temporarily related to starting HAART, not explained by new infection or drug toxicity
- Occurs weeks to months after initiating HAART
- Usually inflammatory, not microbiologic
- Reactivation of antigen-specific T-cell mediated immunity with ART
- “Unmasking IRIS” – activation of latent TB
- “Paradoxical IRIS” – symptomatic relapse of previously successfully treated infection

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Immune Reconstitution Syndrome (IRS)

- Thailand - 153 symptomatic children with CD4 counts < 15% at onset of ART
- 9/153 developed IRS related to (NTM) nontuberculous mycobacterial infection
- Median time to onset was 4 weeks
- *Mycobacterium scrofulaceum, avium, kansasii*
- SC nodules, lung, mesenteric LN

Puthanakit et al. IRS and NTM in children. *PIDJ* 25(7):645, 2006.

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Initiation of HAART with an Acute OI

- Initiate HAART – improve immune function
- Potential for IRIS / IRS syndromes
- Potential drug-drug interactions
- Potential additive toxicities
- Difficulty distinguishing between these

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Initiation of HAART with an Acute OI

- Risk of death during period of delay
- In US, risk of death in a 2 month delay is low
- In resource-limited countries with advanced HIV and higher OI-specific antigenic burdens – higher mortality with delays
- Systemic infection versus local infection
- IRIS events – morbidity, not mortality
- Effective treatment for the infection – no - cryptosporidiosis, microsporidiosis, PML, KS – start ARVs
- TB, MAC, PCP, cryptococcal meningitis – delay ARVs until therapeutic response

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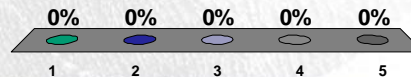
Case # 3

- A 13 year old male, recently under the care of his grandmother because of the death of his mother secondary to AIDS
- Grandmother never knew his HIV status, but the patient says he knew, but never took his medicines
- Patient has fevers, sweats, fatigue, weight loss, occasional diarrhea, intermittent abdominal pain and hepatosplenomegaly
- He has anemia, leukopenia and thrombocytopenia, but his viral load and CD4 counts are not back yet

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What interventions should you offer this patient now?

1. Restart his previous ARVs
2. Treatment for MAC
3. Additional work-up to confirm your diagnosis
4. Re-evaluate his ARVs (past history, viral load, resistance testing, and potential drug interactions)
5. 2 + 3 + 4



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Mycobacterium avium Complex MAC Disease

- *M. avium, intracellulare, paratuberculosis*
- 0.14-0.2 cases /100 patient years, 2000-04
- Definitive diagnosis – culture of organism from blood or biopsy from a normally sterile site (BM, LN, other tissues)
- Initial empiric therapy with ≥ 2 drugs for 2 weeks before restarting HAART
- 1st line – clarithromycin plus ethambutol, rifabutin if OK with planned ARTs
- 2nd line – azithromycin, amikacin, a quinolone
- Duration – 3, 6 months or 12 months if “failure”

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Prevention of MAC Disease

- Prevent exposure – ubiquitous in environment
- Primary prevention – preserve immune function
- Primary prophylaxis
 - >6 years -<100 CD4, <15%
 - 2-5 years -<200 CD4, < 15%
 - 1-2 years -<500 CD4, < 15%
 - < 1 year -<750 CD4, < 15%
- Medications – clarithromycin, or azithromycin
- Discontinue prophylaxis if > 2 years old, asymptomatic for MAC with response to ART and CD4 counts greater than target #s for initiating prophylaxis, for >6 months
- Secondary prophylaxis similar to primary

Guidelines June 20, 2008. page 151, Table #3.

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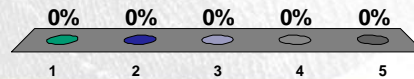
Case # 4

- A 7 week old infant is admitted to the ICU because of bilateral rales, tachypnea RR=60, respiratory distress, hypoxia
- The maternal grandmother brought the child in because he was not feeding well, but no vomiting or diarrhea and his mother had been off for three days
- You suspect PCP or *Pneumocystis jiroveci* pneumonia

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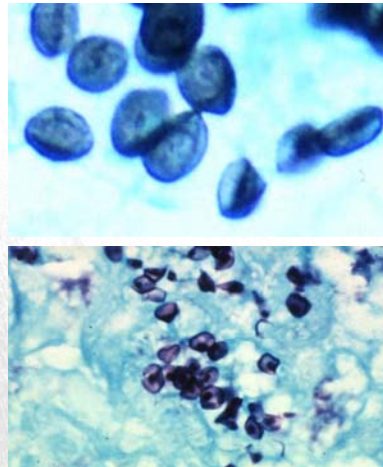
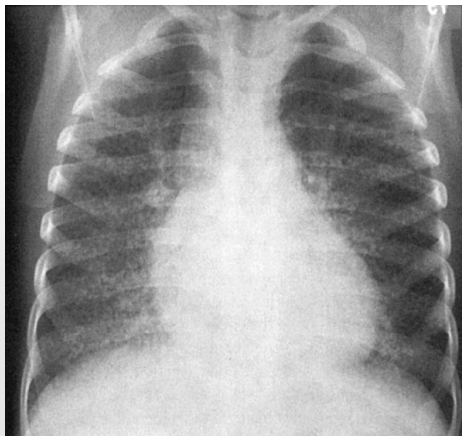
What could convince you this is not PCP Pneumonia?

1. Grandmother telling you her daughter tested negative for HIV in pregnancy
2. Mild perihilar infiltrates on CXR
3. A "sputum", taken immediately after intubation, is negative for PCP
4. The child has not had vomiting
5. None of the above



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PCP in an Infant



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Diagnosis of PCP

- 4 clinical variables independently associated with PCP:
- Age < 6 months
- Respiratory rate > 59 per minute
- Arterial percentage hemoglobin saturation (SaO₂) ≤ 92%
- Absence of vomiting
- ?5th variable – high plasma HIV RNA level

Fatti et al. Clinical Indicators of PCP. Int J Inf Dis 10:282-5, 2006.

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PCP in HIV + Children

- *Pneumocystis jiroveci* – fungus (DNA), features of protozoa (trophozoite, sporozoite, cyst)
- Most common AIDS defining illness in children
- Declining rates of PCP 25/1000 HIV + children in 1994, 18/1000 in 1996, 6/1000 in 2001.
(Morris et al. Epidemiology of PCP Emerg Inf Dis 10:1713, 2004)
- LDH elevation is not specific
- CXR – diffuse “ground-glass”, reticulogranular
- Demonstrate the organism – induced sputum, nasogastric aspirate, BAL, transbronchial or open-lung biopsy
- Stains – Gomori’s methenamine-silver, toluidine blue, Giemsa, “Diff-Quick”, Wright’s stain and monoclonal immunofluorescent antibodies

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Treating PCP in Children

- **TMP-SMX** – 15-20mg TMP/kg/day IV divided TID to QID for 21 days (oral if possible)
- **Pentamidine IV** – if failure or toxicity, 4mg/kg/dose once daily
- **Atovaquone, Dapsone/trimethoprim, Clindamycin/primaquine** (check G6PD)
- **Corticosteroids** – for moderate to severe disease, (PaO₂ < 70mmHg, Aa gradient >35mmHg) methylprednisolone or prednisone with a taper over 21 days
- **Surfactant?**

Sleasman JW. 1993, Bye MR. 1994, McLaughlin GE. 1995, Creery WE. 1997.

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Prevention of PCP

- **Preventing exposure** – human to human, airborne, ?isolation vs prophylaxis
- **Primary prophylaxis** – 4-6 weeks of age thru 1 year, reassess, use age specific cutoffs, 1-5 years <15% or <500 CD4 cells, ≥6 years < 15% or < 200 CD4 cells
- Exposed infants with 2 negative HIV DNA PCR tests @ ≥2 weeks and a 2nd @ ≥4 weeks, don't start prophylaxis for "**presumptive definition of uninfected**"
- **Indeterminate status** at 6-8 weeks – start prophylaxis
- **Secondary prophylaxis** recommended – same CD4 cutoffs
- **Discontinuation of prophylaxis** – immune reconstitution to age specific cutoffs for > 6 months

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Prevention of PCP

- **TMP-SMX 150mg/M²/day divided BID on 3 consecutive days or every other day**
- **Dapsone 2mg/kg (max 100mg) PO daily or 4mg/kg (max 200mg) PO weekly**
- **Atovaquone 30mg/kg PO daily for 1-3 months or >24 months of age and 45mg/kg PO daily for 4-24 months of age**
- **Aerosolized Pentamidine – 300mg nebulized via “Respigard II™” monthly for older children**

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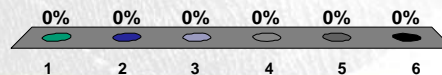
Case # 5

- **A 16 year old HIV + female reports an episode of intensely red vaginal irritation after being given antibiotics in the ER for a recent episode of “cold – sinusitis”**
- **The vaginitis improved with Nystatin vaginal tablets for 14 days and 2 doses of fluconazole 150mg PO on days #1 and 7**
- **Now she reports “heartburn” decreased appetite and not wanting to eat sandwiches or meat**

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What should you do for this patient?

1. Start fluconazole as empiric therapy for Candidal Esophagitis
2. Barium swallow
3. Endoscopy
4. Endoscopy + biopsy to exclude other co-infections
5. Start Amphotericin B or one of its lipid preparations empirically
6. Do 1 + 4



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Esophageal Candidiasis



- Risk factors include: CD4 counts < 100, high viral load, neutropenia (<500) within 4 weeks
- Symptoms include: odynophagia, dysphagia, retrosternal pain, (kids – nausea, vomiting, weight loss), +- oropharyngeal candidiasis
- Diagnosis: barium swallow - cobblestoning, endoscopy, culture, KOH, biopsy – to exclude co-infections

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Esophageal Candidiasis

- Empiric therapy for presumed candidiasis
- Oral or intravenous fluconazole 6mg/kg/day, 1st day and then 3mg/kg/day for 14 - 21 days
- Oral itraconazole solutions
- Intravenous Voriconazole (dosing?) or Posaconazole (other azoles)
- Anidulafungin, Micafungin, Caspofungin (echinocandins)
- Amphotericin B and lipid formulations of Amphotericin B for resistance

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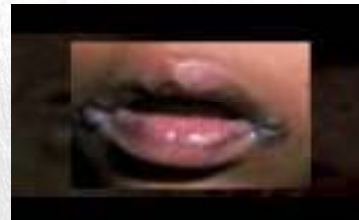
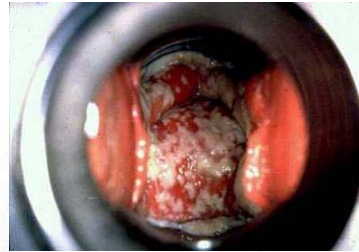
Candidiasis in HIV Positive Children



- Candida species most common fungal infection in HIV + kids
- Oral thrush and diaper dermatitis affects 50-85% of HIV + children
- OPC, diaper dermatitis, vulvovaginitis, esophagitis
- Esophageal and tracheobroncheal candidiasis 1.2 /100 pt. years pre-HAART decreased to 0.8 (2001-04)
- Rarely - candidemia, meningitis, endocarditis, renal disease, endophthalmitis, hepatosplenic disease

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Candida



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Candida Prevention

- **Prevention of Exposure** – commensal mucosal organism
- **Primary prophylaxis** – not recommended routinely
- **Secondary prophylaxis** – not recommended because treatment is usually effective, and the risk of resistance, drug interactions and cost
- **Secondary prophylaxis** – consider it for severe immune suppression and severe or invasive recurrences

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Case # 6

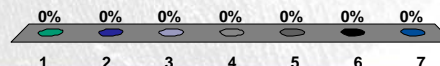
- A 9 year old HIV + AA boy is living with Dad over the summer
- Laboratory testing at the end of school showed a viral load of 7,000, CD4 21%, 323 and a WBC count of 2,800 with 17% PMNs, 55% lymphs, 18% monos, 9% eos
- The boy develops a “bad cold” with wheezing, + cough
- The Dad’s brother died of asthma
- The acute care physician prescribes antibiotics, inhaled albuterol and oral prednisone for 21 days for “Bronchitis-Asthma”
- On day #19 of treatment the boy develops a fever, dyspnea and pleuritic pain

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Invasive Pulmonary Aspergillosis

What are the most important risk factors?

1. Viral load of 7,000
2. He was on antibiotics
3. He was taking prednisone for >14 days
4. He was neutropenic
5. 2 + 3 + 4
6. 1 + 3
7. 2 + 4



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Aspergillosis

- Ubiquitous mold - rare but often lethal
- Incidence in pediatric HIV was 1.5-3% in the pre-HAART era (less now)
- Risk factors include: low CD4 count, neutropenia, corticosteroid use, concurrent malignancy, chemotherapy, broad spectrum antibiotic use, previous respiratory illness and HIV-related phagocyte abnormalities

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Aspergillosis in HIV + Children



- Invasive pulmonary disease
- Necrotizing or pseudomembranous tracheobronchitis
- CNS – abscess, meningitis
- Cutaneous – IV , tapes and board
- Sinusitis
- Otitis media, Mastoiditis

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Aspergillosis Treatment

- Voriconazole - ? Optimal dose, higher doses
- Voriconazole 6-8mg/kg IV or 8mg/kg PO every 12 hrs X 2, then 7mg/kg BID for 12 weeks
- CYP450 enzyme metabolism – 2C19, 2C9, 3A4
- Drug interactions – PIs and efavirenz
- Side effects – visual disturbances, increased LFTS, occasional skin rash
- Amphotericin B or it's lipid formulations
- Caspofungin - IV

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Aspergillosis Prevention

- Limit or eliminate risk factors (neutropenia, antibiotics, corticosteroids)
- Exclude plants, fruits and flowers
- “Neutropenic” diet
- Primary Prophylaxis – not recommended
- Secondary Prophylaxis – continue antifungal therapy thru the period of greatest risk – steroids, neutropenia; otherwise it is not recommended

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Fungal Infections in HIV Positive Children

- **Coccidioidomycosis**
 - Pulmonary – fever, malaise, chest pain, variable – cough, hemoptysis
 - Meningitis – headaches, altered sensorium, vomiting, focal neurologic signs, hydrocephalus
 - Disseminated – LA, skin nodules, peritonitis, liver abnormalities
- **Cryptococcosis**
 - < 0.1 per 100 pt. years
 - Meningoencephalitis – fever and subacute headaches, nuchal rigidity, photophobia and focal neurologic signs
 - Disseminated – cutaneous papules (like molluscum), nodules, ulcers, plaques
 - Pulmonary without dissemination is rare in children

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Prevention of Fungal Infections in HIV Positive Children

- **Coccidioidomycosis**
 - Avoid disturbing contaminated soil
 - Primary prophylaxis not recommended – low incidence, drug interactions and resistance
 - Secondary prophylaxis – fluconazole or itraconazole – lifelong - ? Discontinue prophylaxis?
- **Cryptococcosis**
 - Prevention – avoid birds and “public” water sources
 - Primary prophylaxis – not recommended
 - Secondary prophylaxis – fluconazole (better than itraconazole)
 - Discontinuing prophylaxis – at age appropriate cutoffs for > 6 months

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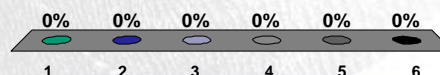
Case # 7

- A newly diagnosed 28 month old HIV + child with his aunt (in foster care)
- She tells you he was diagnosed with HIV last month, after he was hospitalized 3 times with pneumonia since Thanksgiving and was admitted last month for a “Strept bacteria” in his blood
- She doesn’t know about his immunizations and his mother is in jail

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What should you do next?

1. Start IVIG
2. Immunize him all over again
3. Check quantitative IgG, Pneumococcal, Hib, Hep B, measles and VZV titers
4. Start Septra prophylaxis
5. 3 + 4
6. 1 + 2



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Serious Bacterial Infections in HIV + Children

- Pneumonia – 11 per 100 child-years (pre-HAART)
– 2 - 3.1 per 100 child-years (HAART)
- Bacteremia – 3 per 100 child-years
– .35 - .37 per 100 child-years (HAART)*
- UTI – 2 per 100 child-years
- Osteomyelitis, meningitis, abscess, septic arthritis
– < 0.2 per 100 child-years
- Otitis media, sinusitis
– 17- 85 per 100 child-years
– 2.9 – 3.5 per 100 child-years (HAART)*

* Still higher than in HIV negative children

Guidelines for OIs in Children, 6/20/08

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Serious Bacterial Infections in HIV + Children

- *Streptococcus pneumoniae*
- *Haemophilus influenzae type b*
- *Neisseria meningitidis* - ? Increased risk
- Gram-negative bacteremia – *Ps. Aeruginosa*, nontyphoidal *Salmonella*, *Escherichia coli*
- Central venous catheter – increased risk, incidence similar to children with cancer
- In resource-limited countries – increased risk with advanced maternal disease and maternal smoking in pregnancy

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Prevention of Serious Bacterial Infections in HIV + Children

- **Immunization** – Prevnar, Pneumovax, Hib, MCV4, “Flu”
Guidelines for Prevention of OIs in Children immunization tables on pages 195-196, June 20, 2008.
- **Food** – avoid raw or undercooked foods: eggs, poultry, meat, seafood / shellfish and raw seed sprouts
(Vit A and zinc supplements in resource-limited countries)
- **Pets** – avoid dogs or cats < 6 months or stray animals, avoid reptiles, chicks and ducklings, avoid sick animals
- **Travel** – avoid tap water or ice from tap water, unpasteurized dairy products, items sold by street vendors

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Prevention of Serious Bacterial Infections in HIV + Children

- **Primary prophylaxis** – not recommended
- **IVIG** – only for hypogammaglobulinemia or functional antibody deficiency
- **Secondary prevention** – check the specific antibody status and considered re-immunization or IVIG for hypogammaglobulinemia and recurrences

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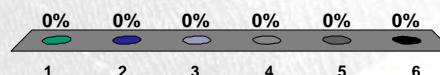
Case # 8

- A 13 year old female with AIDS, CD4 counts consistently < 100 goes to her Aunt's home in Georgia for summer vacation
- She and her cousins favorite thing to do there is to go to the water park
- When she returns, her mother calls to say her daughter stopped taking her ARVs, while she was away and has had watery diarrhea without blood/mucus for 6 weeks and has lost weight
- You schedule her for the next clinic, and get them to submit multiple stool cultures for specific organisms, samples for O&P and get blood cultures done before they come to clinic
- Two days before clinic she develops fever, vomiting and right upper quadrant abdominal pain

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How should you do next for this patient?

1. Start ciprofloxacin and metronidazole
2. Start albendazole
3. Start Nitazoxanide
4. Wait for the cultures
5. Evaluate her for cholecystitis / cholangitis
6. 4 + 5



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Diarrhea in HIV + Children

Legend:
 ▲ = Infective Stage
 ▲ = Diagnostic Stage

- Salmonella
- Shigella
- Yersinia
- E. coli
- Campylobacter
- Clostridium difficile
- MAC
- Cryptosporidium
- Microsporidium
- Isospora Belli
- Giardia
- CMV enteritis
- Rotavirus
- Enteric Adenovirus

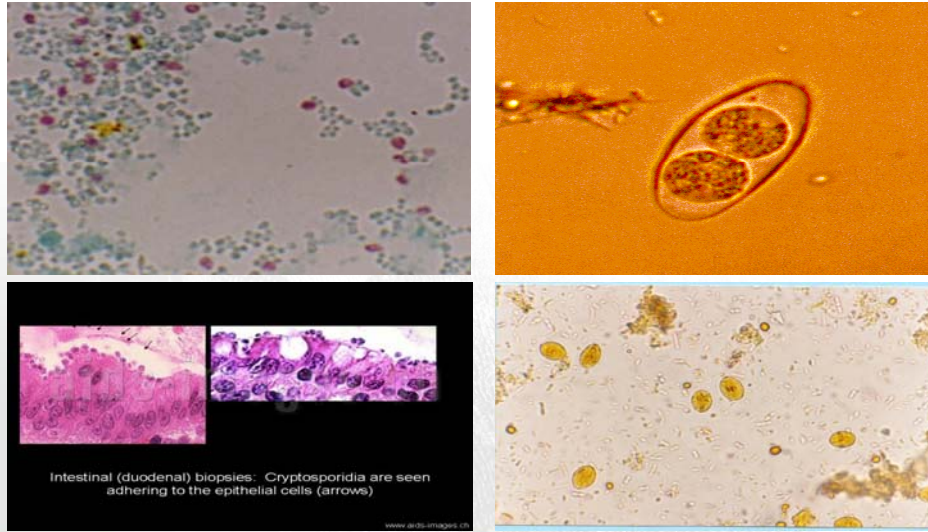
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Diarrhea in HIV + Children

- Most episodes of acute diarrhea will not require diagnostic evaluation
- Work-up severe or persistent symptoms, fever, blood/mucus in the stool, severe abdominal pain, weight loss
- The clinical picture should guide the evaluation – enteritis, ileocolitis, dysentery, (or other symptoms of cholangitis, hepatitis, or peritonitis)
- Consider all the organisms on the etiologic list
- Consider colonoscopy (+- biopsy) for dysentery
- Consider upper endoscopy (+- biopsy) for persistent diarrhea of unknown cause

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Etiologic Agents of Diarrhea



Intestinal (duodenal) biopsies: Cryptosporidia are seen adhering to the epithelial cells (arrows)

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Protozoal Parasites in HIV + Children

- **Cryptosporidiosis**
 - Fecal-oral, person-to-person, foodborne, recreational water
 - Persistent watery, nonbloody diarrhea > 2 weeks, cramping abdominal pain, fatigue, anorexia, weight loss, +/- fever or vomiting = enteritis
 - Acalculous cholecystitis or sclerosing cholangitis, rarely pancreatitis or dissemination
 - Oocysts in stool or tissue, sucrose-flotation, formalin-ethyl acetate method, monoclonal-Ab, Ag - Elisa
- **Microsporidiosis**
 - Multiple species – *Enterocytozoon bienersi*, *Encephalitozoon intestinalis*
 - Fecal-oral, contaminated food or water
 - Acute and chronic diarrhea, hepatitis, peritonitis, keratoconjunctivitis, myositis, cholangitis, sinusitis, encephalitis and disseminated disease
 - Thin smear of unconcentrated stool-formalin suspension, duodenal aspirate – trichrome stain, endoscopic biopsy

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Treatment of Protozoal Parasites in HIV + Children

- **Cryptosporidiosis**
- No consistently effective therapy is available
- Nitazoxanide – 100mg PO BID for 1-3 years, 200mg BID for 4-11 years, 500mg BID for >12 years
(Rossignol 1998, 2001; Amadi 2000)
- Paromycin - no
- Azithromycin – 10 days
(Hicks P. J Peds 1996)
- **Microsporidiosis**
- Albendazole is effective against many Microsporidia, but not *E. bienewisi* or *V. corneae*
- Fumagillin (TNP-470) – experimental, but no data in HIV + pts
(Didier PJ, Fumagillin AAC 50:2146, 2006.)
- Metronidazole and atovaquone are not active for these

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Prevention of Protozoal Parasites in HIV + Children

- **Prevention** – **block routes of transmission** by hand-washing, avoiding pets / animals, water from lakes, rivers, recreational water, avoiding unpasteurized drinks requiring refrigeration
- **Prevention** – prevent severe immune suppression with effective ARV therapy
- **Primary prophylaxis** – not recommended
- **Secondary Prophylaxis** – not recommended

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Toxoplasmosis in Children

- Congenital 1 case per 1,000-12,000 births US
- Primary Toxo in pregnancy – risk of *in utero* infection 29% after primary infection, higher in 2nd, 3rd trimesters
- Risk of congenital infection in HIV+, Toxo + pregnant women 1-3%, especially with severe immunosuppression
- Pediatric Toxo – rare
- CNS Toxo – 5/2767 (0.2%) in PACTG 219C
- Ocular Toxo – rare, and usually in association with CNS,
- Chorioretinitis – visual loss and white retinal lesions
- Systemic – pneumonitis, hepatitis, myocarditis/opathy

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Diagnosis of Toxoplasmosis

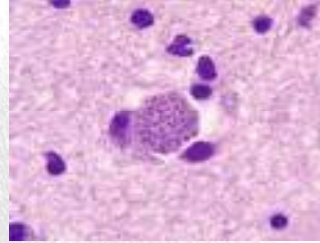
- Congenital Toxo – difficult to diagnose – serology – Ig – M, A, E and PCR body fluids
- Do not routinely screen HIV positive children (screen adults, ? Older children)
- CNS Toxo – space occupying lesion on imaging plus serology (MRI > CT), brain biopsy
- Chorioretinitis – retinoscopy plus serology



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Treatment of Toxoplasmosis in HIV

- CNS, ocular or systemic infection – pyrimethamine + sulfadiazine (+ leucovorin) for 6 or more weeks (alternative to sulfadiazine is clindamycin or azithromycin)
- In adults alternatives include atovaquone + pyrimethamine + leucovorin or atovaquone + sulfadiazine (not studied in children)
- CNS disease with CSF protein > 1000 mg/dL or focal lesions and mass effect – use corticosteroids



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Toxoplasmosis Prevention

- **Prevent Exposure** – raw or undercooked meat, washing hands after working with soil, cats or cat litter-boxes, test the cats
- **Primary Prophylaxis** – for severe immune suppression (adults < 100 CD4, children <15%) 1) septria, 2) dapsone-pyrimethamine, 3) atovaquone (not –dapsone, azithromycin, clarithromycin, pentamidine)
- **Discontinuing Prophylaxis** – no data in children, OK with immune reconstitution for > 6 months above age appropriate levels – 1-5 years old > 15%, >=6 years old >15% or >200CD4 cells
- **Secondary Prophylaxis** – 1) pyrimethamine + sulfadiazine, (OK – PCP) 2) pyrimethamine + clindamycin, 3) atovaquone +/- pyrimethamine, 4) intolerant of other regimens may consider - Septra

Guidelines for OIs Prevention June 20, 2008. page 151, Table #3.

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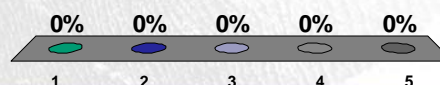
Case # 9

- A 19 year old HIV + female gains 20 lbs in 3 months, and is under the stress of going to college, a new boyfriend and living with her grandparents
- She comes in complaining of mouth sores, and decreased eating (no chest pain or dysphagia)
- She appears to have thrush and is given oral nystatin and fluconazole
- That same day, her labs show her first viral load > 50 (13,500) in 2 years and a decrease in CD4 counts to 13%, 247
- 7 days into her therapy she still is complaining of mouth sores, swollen gums, decreased eating and swelling beneath her jaw

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What is on your differential diagnosis list now?

1. HSV
2. Resistant candida
3. Fusobacterium necrophorum
4. Coxsackie virus
5. All of the above



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Primary Herpetic Gingivostomatitis



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HSV 1 and 2

- **Developed countries: HSV-1 acquired at younger ages in urban poor populations (70-80% seropositive by the age of 20) compared with other populations (30-40%)**
- **Increasing HSV-1 seroprevalence with age – 26% in 6-7 year olds and 36% in 12-13 year olds and approaches 60% in adults**

Xu F et al. HSV in children in US. J Peds 2007. 151:374.

- **HSV-2 seroprevalence also increases with age from 2% in 14-19 year olds to 26% in 40-49 year olds (average 17% between 14-49 years old)**

Xu F et al. HSV Trends in US. JAMA 2006. 296:964-73.

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Clinical Manifestations

- | | |
|---|---|
| <ul style="list-style-type: none"> • <u>HSV 1</u> • Neonatal Herpes • Gingivostomatitis, oral labial disease* • Local or generalized skin lesions • Disseminated disease+ • Visceral+ • Esophagitis • Keratitis+, Herpetic Whitlow • CNS+ | <ul style="list-style-type: none"> • <u>HSV 2</u> • Herpes Genitalis* • Neonatal Herpes+ (SEM, CNS or disseminated) • Local or generalized skin lesions • CNS+ • Disseminated+ • Esophagitis • Keratitis+, Herpetic Whitlow |
|---|---|
- * Most common, + most morbidity / mortality

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HSV Treatment

- Acyclovir po (50% bioavailable) or IV
- Valacyclovir – limited data in children
- Famciclovir - limited data and no pediatric formulation
- Keratoconjunctivitis - Trifluridine ophthalmic + acyclovir
- Acyclovir-resistant HSV - Foscarnet IV
- Topical Trifluridine or Cidofovir
- Acyclovir and foscarnet resistance - Cidofovir

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HSV Prevention

- **Prevent Exposure** – elective cesarean, decrease contact, treatment of source case
- **Primary Prophylaxis** – not recommended
- **Secondary Prophylaxis** – after neonatal HSV – especially SEM, otherwise – usually not recommended, except in situations with frequent recurrences (3-6 severe episodes in a year), CNS or eye involvement

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CMV in HIV + Children

- HIV+ CMV+ women shed CMV from cervix (52-59% compared with 14-35% in HIV- women)
- HIV+ CMV+ infants 33% shed CMV virus, (~60% with AIDS), and 15-20% shed CMV in CMV+ HIV-exposed infants
- Rate of CMV *in utero* infection was 4.5% in 440 HIV + women (compared with <2% in general population)
- CMV = 8-10% of AIDS-defining illness (pre-HAART)
- In 3000 HIV+ children CMV retinitis was 0.5 cases per 100 child years and 0.2 events of other CMV disease per 100 child years in the pre HAART years.
- Non-ocular CMV 1.4 per child-years (pre-HAART) and 0.1 per 100 child-years (post-HAART) PACTS study

[Guidelines for OIs in Children, 6/20/08, pg 92.](#)

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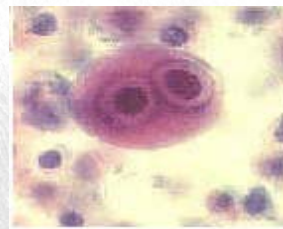
CMV in HIV + Children

- HIV+, CMV+ co-infected children show accelerated progression of HIV disease compared with CMV- children (relative risk = 2.6 [CI1.1-6.0])
- CMV retinitis is the most frequent severe manifestation
- Extra-ocular disease – predominantly nonspecific symptoms
- Extra-ocular disease – lung (co-infection), liver, GI tract, pancreas, kidney, CNS (encephalopathy, myelitis, polyradiculopathy)

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Diagnosis of CMV

- Cell culture peripheral blood leukocytes, body fluids (urine, BAL), tissues
- DNA PCR – CSF, blood more significant for invasive disease
- Biopsy tissue – liver, lung, endoscopic from GI tract – culture, immunostaining, histology – "owl's eye intranuclear inclusions"



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Treatment of CMV

- **CMV retinitis** – treat in collaboration with an experienced ophthalmologist
- **Ganciclovir* IV, valganciclovir po, foscarnet* IV, cidofovir* IV, intravitreal injections* and ganciclovir sustained intraocular implant (>3 years of age)**
- **Valganciclovir – extemporaneously compounded liquid - ? Pharmacokinetics**
- **Systemic or CNS CMV disease – ganciclovir (CSF levels 28-70% of plasma level, brain concentrations 38% of plasma level) , foscarnet, cidofovir or use of combined therapy ganciclovir + foscarnet ?**

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Prevention of CMV

- **Preventing Exposure** – CMV negative blood, hand-washing especially in child- care situations, screen CMV Ab yearly for CMV- children with severe immune suppression,
- **Preventing Disease** - screen CMV + children with severe immune suppression q 6 months with dilated retinal exam, advise re: possible CMV symptoms, maintain immune status with ARV therapy
- **Primary Prophylaxis** – not recommended (valganciclovir if large enough, severe immune suppression and CMV+)
- **Secondary Prophylaxis** – IV ganciclovir or foscarnet, and oral valganciclovir for older children (dosing) Ages 1-6 years CD4 cells < 200, >=6 years old <100 CD4 cells
- **Discontinuing Prophylaxis** – little data in children, OK with age appropriate immune reconstitution of CD4 counts for 6 months

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VZV in HIV+ Children

- Varicella is primary infection and Zoster is a secondary / reactivation infection in individuals with previous VZV infection
- HIV+ children with low CD 4 counts (15%) with primary varicella infection; the rate of subsequent zoster was about 70%.
- Zoster incidence in HIV+ immune compromised children with varicella – 467 per 1000 child-years vs. 98 per 1000 person-years in HIV infected adults and 25 per 1000 child-years in children with leukemia.
- CD4 counts correlate with frequency of Zoster recurrences
- Transient increase in Zoster after institution of PIs

Gershon JID 1997, Derryck PIDJ 1998, von Seidlein J Peds 1996, Martinez CID 1998

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VZV in HIV+ Children

- Longer duration and higher rates of complications
- Persistent lesions are often atypical, lack a vesicular component
- Disseminated zoster appears like varicella without visceral involvement
- Multiple episodes of dermatomal disease
- Progressive outer retinal necrosis – VZV associated with low CD4 counts and dermatomal zoster – rapid visual loss but little or no ocular inflammation
- Unilateral vesicular rashes

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VZV in HIV+ Children

- **Diagnosis**
- Clinical
- Direct immunofluorescence of VZV Ag
- Cell culture from vesicular fluid or ulcer base
- VZV PCR
- Serology (for primary infection and usually late diagnosis)
- **Treatment**
- IV acyclovir – 10-15 mg/kg q8 hours for 7-14 days or longer
- Oral acyclovir, valacyclovir, famciclovir
- Acyclovir-resistant VZV - foscarnet

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Prevention of VZV

- **Preventing Exposure** – avoid exposure to individuals with VZV
- **Preventing Disease** - **Varicella Vaccine X 2** when CD4 % >15 (Zoster from Oka strain = vaccine has not been described in HIV+ children), **VariZIG** (1-800-843-7477 or <http://www.fffenterprises.com> per IND) or **IVIG** 400mg/kg once within 96 hours of exposure, Acyclovir – no data
- **Secondary Prophylaxis** – Zoster vaccine – no data in HIV+ individuals adults or children

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HPV in HIV+ Children

- HPV infection in HIV negative youth demonstrates spontaneous regression in 80-90% cases
Moscicki et al. J Peds 1998. Ho et al. NEJM 1998.
- Persistent infection with high-risk HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) is associated with increased risk of developing cervical and intraepithelial neoplasia and risk for cervical, vulvovaginal and anal carcinoma (these cancers are found at higher rates in HIV + persons)
Frisch et al. JNCI 2000. 92:1500-10.
- 33% of HPV infected youth with HIV progressed to high-grade squamous intraepithelial lesion (HSIL) within 3 years of observation
Moscicki et al. 2004. JID 190:1413-21.

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HPV in HIV+ Children

- | | |
|---|---|
| <ul style="list-style-type: none"> • <u>Diagnosis</u> • Clinical – condyloma accuminatum, anogenital lesions • PAP test • Colposcopy or high-resolution anoscopy (biopsy for histology) • HPV DNA | <ul style="list-style-type: none"> • <u>Treatment</u> • Standard topical therapy is often ineffective – podofilox, imiquimod, trichloroacetic or bichloroacetic acid podophyllin resin • Veregen, intralesional IF or 5 fluorouracil /epinephrine gel implant, topical cidofovir • Cryotherapy or surgery • Abnormal cytology – CIN - colposcopy and cytology, serial follow-up • Persistent CIN – cryotherapy, laser, cone biopsy, loop electrosurgical excision procedure (LEEP), serial follow-up • Role of HAART? |
|---|---|

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Prevention of HPV

- **Preventing Exposure** – latex condoms
- **Primary Prevention** – HPV Vaccine (for types 16, 18, 6, 11) [HIV negative women – 95% efficacy for preventing HPV infection and high-grade CIN and 99% for genital warts) No studies yet in HIV + persons.
- **Preventing Disease** – for sexually active individuals – PAP screening yearly, Anal HSILs yearly,
- **Secondary Prophylaxis** – no recommendations

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Summary

- **Mantra = Remember that children are different from adults and why / how!**
- **Note the different cutoffs for different levels of immune suppression in children.**
- **Think of the various clinical cases we talked about.**
- **Remember immunizations for prevention.**
- **Check out the resources – coming up in the last 2 slides!**
- **Thank you.**

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Vaccine Preventable Diseases

- **See**
<http://www.cdc.gov/vaccins/recs/schedule/s/default.htm> for immunization schedules.
- **See**
<http://www.cdc.gov/vaccines/pubs/ACIP-list.htm> for recommendations, precautions and contraindications for vaccines.

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Resources

- **Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children. June 20, 2008.**
Recommendations from CDCP, NIH, HIV Medicine Assoc, IDSA, PID Society and AAP.
<http://AIDSinfo.nih.gov>
- **HIV CareLink Vol 9 – Issue 9 August 1, 2008.**
Mirza A. Review of above Guidelines
www.FCAETC.org
- **Clinical Consultation with Pediatric HIV Specialists** www.FCAETC.org or 1-800-933-3413
National Clinicians' Consultation Hotline

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