Respiratory Disorders in Children Infected with HIV and with Other Immunodeficiencies

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Disclosures

- No disclosures

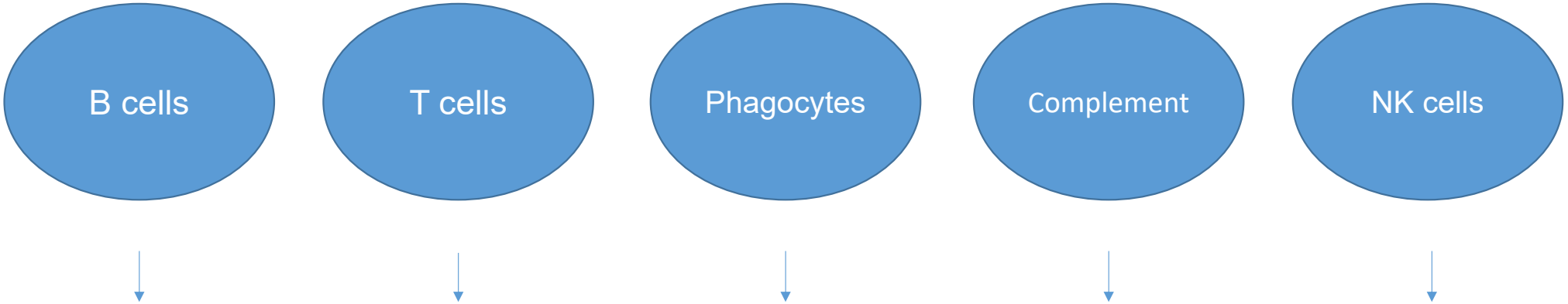
Objectives for the Pediatric Pulmonologist

- Understand the public health lessons that the HIV epidemic provide
- Apply the lessons from HIV infection to other immunodeficiency diseases
- Develop an approach to diagnosis of pulmonary complications associated with immunodeficiency states

Spectrum of Immunocompromised Hosts

- Primary immune deficiencies
  - intrinsic defects in one or more compartments of the immune system
- Secondary immune deficiencies
  - immunosuppressive therapies
  - viral infections – HIV, measles
  - organ and hematopoietic transplant
  - malnutrition
  - severe burns

Pulmonary Manifestations of Immune Deficiencies



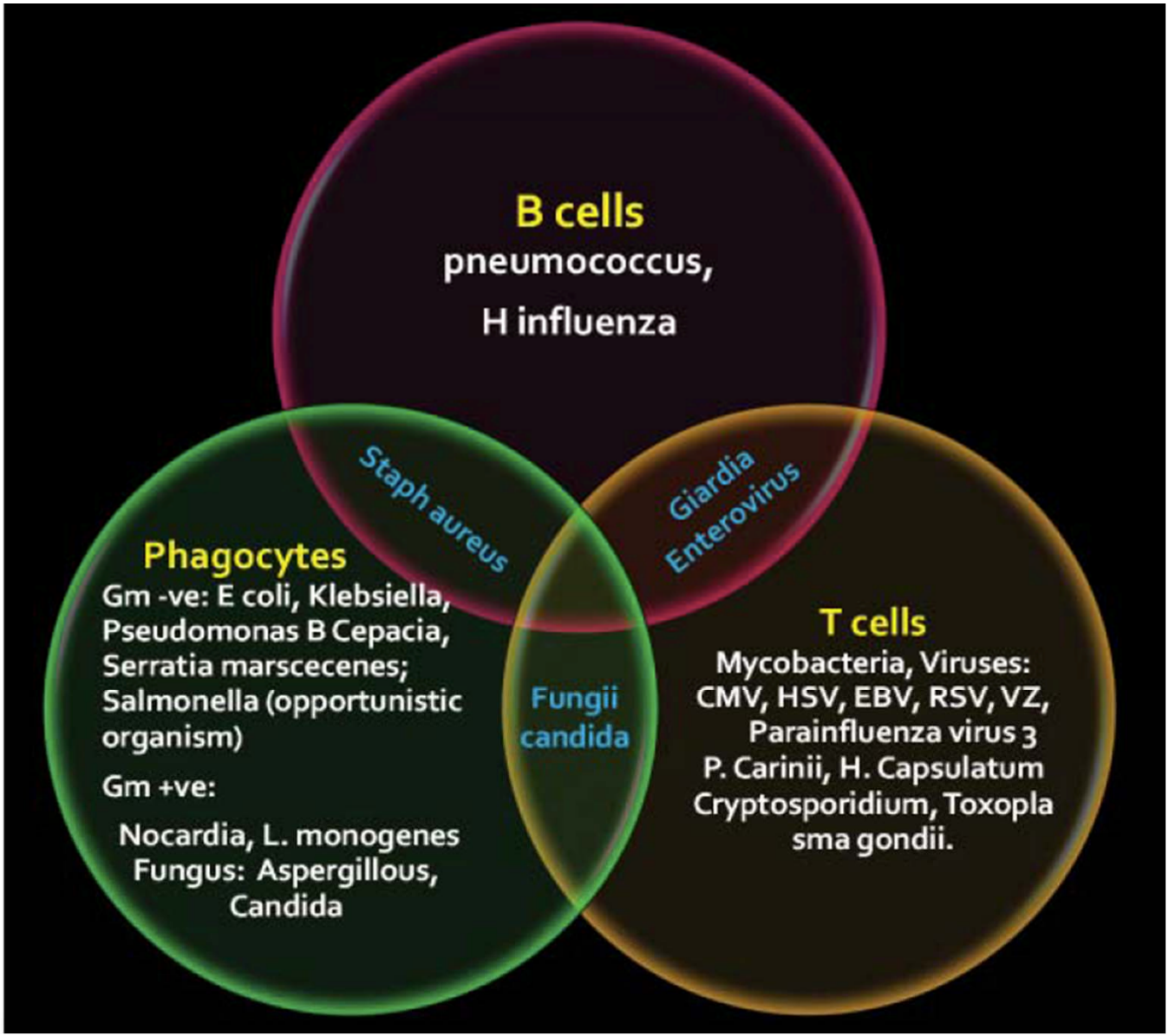
Recurrent respiratory tract infections with encapsulated bacteria

- Severe viral infections
- Fungal infections
- Pneumocystis jiroveci

- Pneumonia
- Infections with catalase positive organisms (CGD)

- Infections with encapsulated bacteria
- Recurrent Neisserial infections

- Herpes virus infections
- Malignancies


B cells
pneumococcus,
H influenza
Staph aureus
Giardia
Enterovirus
Phagocytes
Gm -ve: E coli, Klebsiella, Pseudomonas B Cepacia, Serratia marscecenes; Salmonella (opportunistic organism)
Gm +ve:
Nocardia, L. monogenes
Fungus: Aspergillous, Candida
Fungii
candida
T cells
Mycobacteria, Viruses: CMV, HSV, EBV, RSV, VZ, Parainfluenza virus 3
P. Carinii, H. Capsulatum
Cryptosporidium, Toxoplasma gondii.

Measles and HIV – Mirror Images

- Prevention is the goal
- Immunosuppressive diseases
- Respiratory complications are major causes of morbidity and mortality worldwide
- Political, social and economic factors influence outcome

Importance of a Historical Perspective

- Understand the approach to and management of respiratory problems in immunocompromised children
- Learn from the response to a previously unidentified epidemic
- Past is the present in many areas of the world

Respiratory Disorders and HIV

- Epidemiology
- Pulmonary manifestations of HIV in the pre and post HAART (highly active antiretroviral therapy) era
- Long term pulmonary consequences of HIV infection

Populations of Concern to the Pediatric Pulmonologist

- Children with vertically transmitted HIV infection
- Adolescents with acquired HIV infection
- Children HIV-exposed in utero and uninfected

Etiology and Pathogenesis

- Human immunodeficiency virus (HIV) is a retrovirus
- DNA is synthesized from RNA through reverse transcriptase and integrated into host DNA genome
- Cellular immunity
  - CD4 T lymphocyte is main cellular target
  - Depletion of CD4 cells
- Humoral immunity
  - B cell dysfunction

Transmission

- Perinatal transmission can occur *in utero*, intrapartum and through breast feeding
- Sexual abuse
- Sexual transmission
- Drug abuse
- Blood products

MMWR

June 5, 1981 / 30(21);1-3

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Science

Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)

F Barre-Sinoussi et al. *Science* 20 May 1983:220,868-871

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MMWR

June 24, 1983 / 32(24);309-11

Only 109 (7%) cases have been reported in women.

In addition to the 1,641 reported AIDS cases, **21 infants** with opportunistic infections and unexplained cellular immunodeficiencies have been reported to CDC.

4H Club
The Stigma of AIDS

- Homosexuals (GRID)
- Haitians
- Heroin addicts
- Hemophiliacs

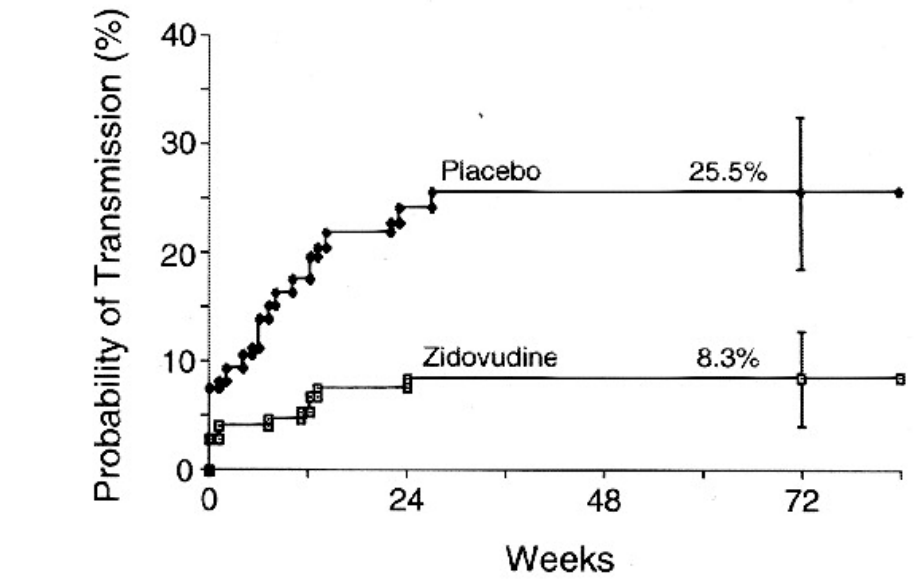
The New England
Journal of Medicine

Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, PH.D., PAVEL KISELEV, PH.D., GWENDOLYN SCOTT, M.D., MARY JO O'SULLIVAN, M.D., RUSSELL VANDYKE, M.D., MOHAMMED BEY, M.D., WILLIAM SHEARER, M.D., PH.D., ROBERT L. JACOBSON, M.D., ELEANOR JIMENEZ, M.D., EDWARD O'NEILL, M.D., BRIGITTE BAZIN, M.D., JEAN-FRANÇOIS DELFRAISSY, M.D., MARY CULNANE, M.S., ROBERT COOMBS, M.D., PH.D., MARY ELKINS, M.S., JACK MOYE, M.D., PAMELA STRATTON, M.D., AND JAMES BALSLEY, M.D., PH.D., FOR THE PEDIATRIC AIDS CLINICAL TRIALS GROUP PROTOCOL 076 STUDY GROUP*

Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment



Connor EM et al. N Engl J Med 1994;331:1173-1180.

2017 Facts

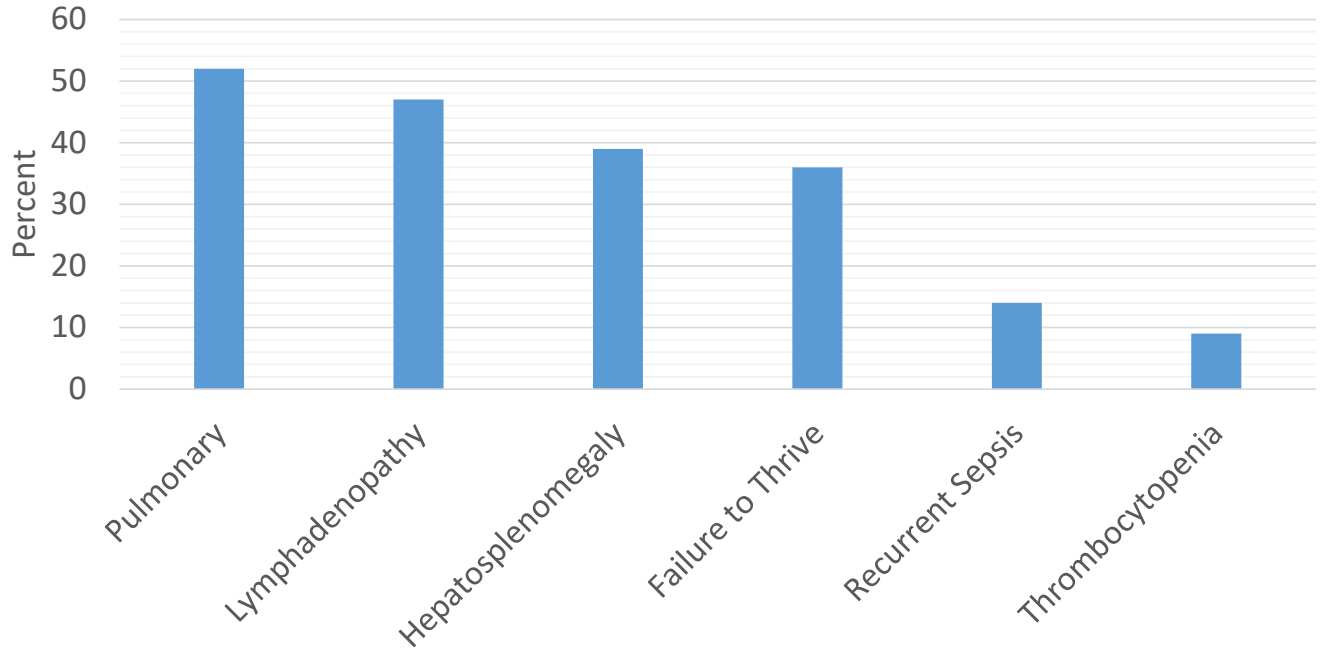
- 1.8 million children* living with HIV worldwide
- 180,000 children became newly infected
- 110,000 children died of AIDS related disease

- 43% of children living with HIV accessed antiretroviral therapy
- New HIV infections declined by 47% since 2010

* Children (<15 years)

Data from UNAIDS | 2018

Initial Presentation of HIV Infection in Pre HAART Era



Marolda J et al. 1991;10:231-235

Pulmonary Disease in pre HAART Era

- 52 children with AIDS and pulmonary disease admitted between 1982 and 1988
- Median age of initial respiratory symptoms – 6 months (range 1-180 months)
- 18 (35%) had respiratory failure and 8 (44%) survived
- PCP and bacterial pneumonia were most common causes of respiratory failure

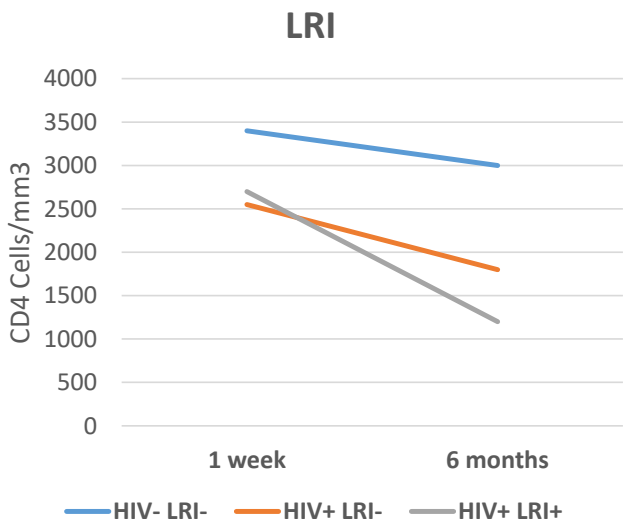
Marolda et al. Pediatr Pulmonol 1989;7:230-234

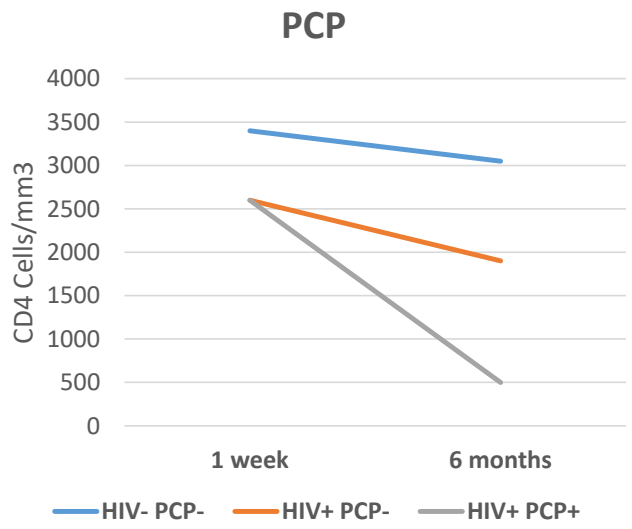
Pulmonary Complications by 12 months in Infants Born to HIV Infected Mothers

	HIV infected N=93	HIV uninfected N=463	P-value
Complication	Rate/100 child-years (95% CI)	Rate/100 child-years (95% CI)	
Pneumonia NOS	15.5 (8.2,26.4)	0.7 (0.2,2.1)	<0.001
Viral pneumonia	7.1 (2.6,15.5)	0 (0.0,0.9)	<0.001
Bacterial pneumonia	3.6 (0.7,10.4)	0.5 (0.1,1.8)	<0.08
PCP	9.5 (4.1,18.7)	0.29 (0.0,1.4)	<0.001
URI	117.7 (88.3,147.1)	104.3 (92.9,115.7)	NS

Kattan et al Pediatr Pulmonol 2001;31:267-276

Rate of Decline of CD4 Cells and Pulmonary Infection





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Impact of HAART on Opportunistic Infections

	Pre-HAART Rate#	Post-HAART Rate*
Complication	Rate/100 child-years (95% CI)	Rate/100 child-years (95% CI)
PCP	1.3 (1.1-1.6)	0.1 (0.04,0.2)
Pneumonia	11.1 (10.3-12.0)	2.2 (1.8,2.6)
Bacteremia	3.3 (2.9-3.8)	0.4 (0.2,0.5)
Disseminated MAC	1.8 (1.5-2.1)	0.1 (0.1,0.3)
Tracheobronchial/ esophageal candidiasis	1.2 (1.0-1.5)	0.1 (0.03-0.2)

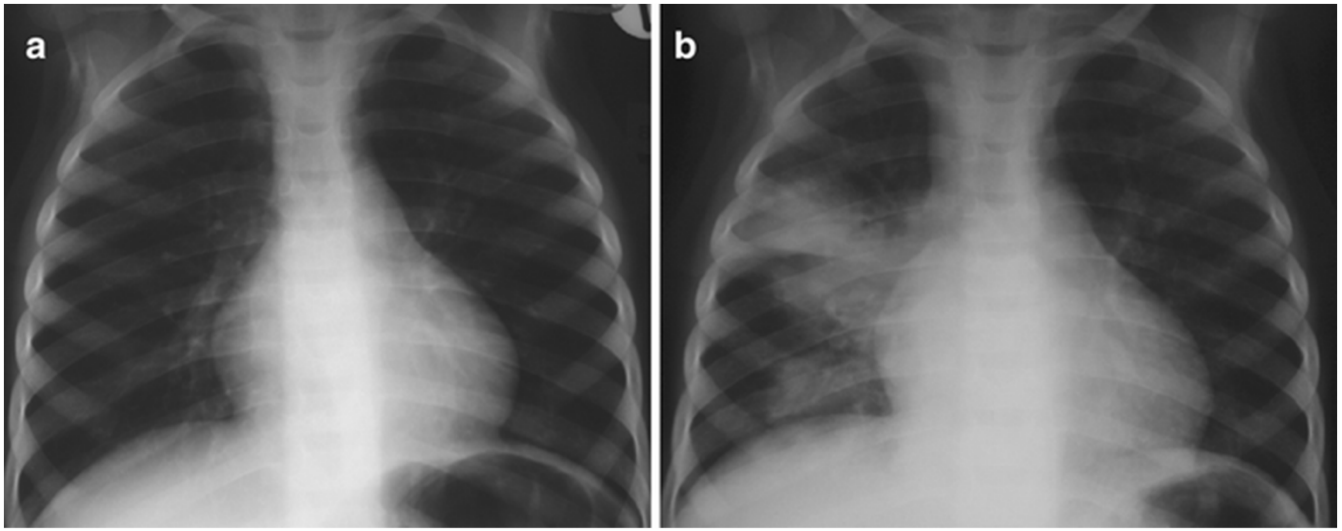
Dankner WD et al. Pediatr Inf Dis J 2001;20:40-48

* Gona P et al. JAMA 2006;296-292-300

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Occurs weeks to months after initiation of HAART
- Florid immune response most commonly directed against mycobacterial antigen
- Paradoxical increase in signs
  - Increasing lymphadenopathy
  - Fever
  - New respiratory infiltrates

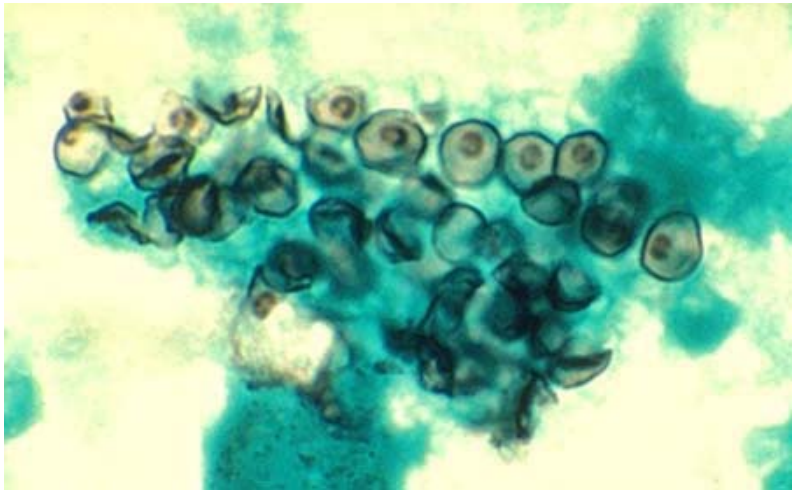
Immune Reconstitution Inflammatory Syndrome



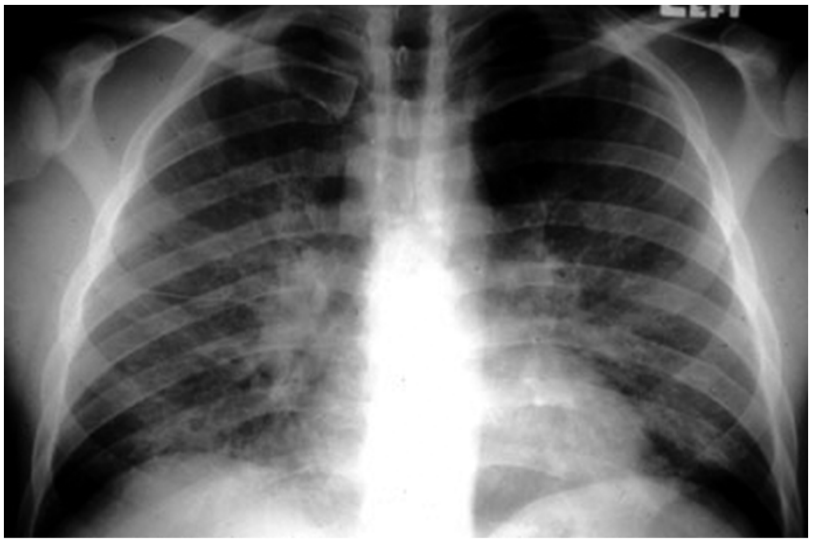
Kilborn, T. & Zampoli, M. Pediatr Radiol (2009) 39: 569

Pneumocyctis Jirovecii Pneumonia

Pneumocystis Jirovecii



TB and HIV



Chronic Lung Disease in HIV

- Bronchiectasis
- Constrictive obliterative bronchiolitis
- Lymphoid interstitial pneumonia
- Asthma

Chronic Radiographic Changes
P2C2 HIV Study Definitions

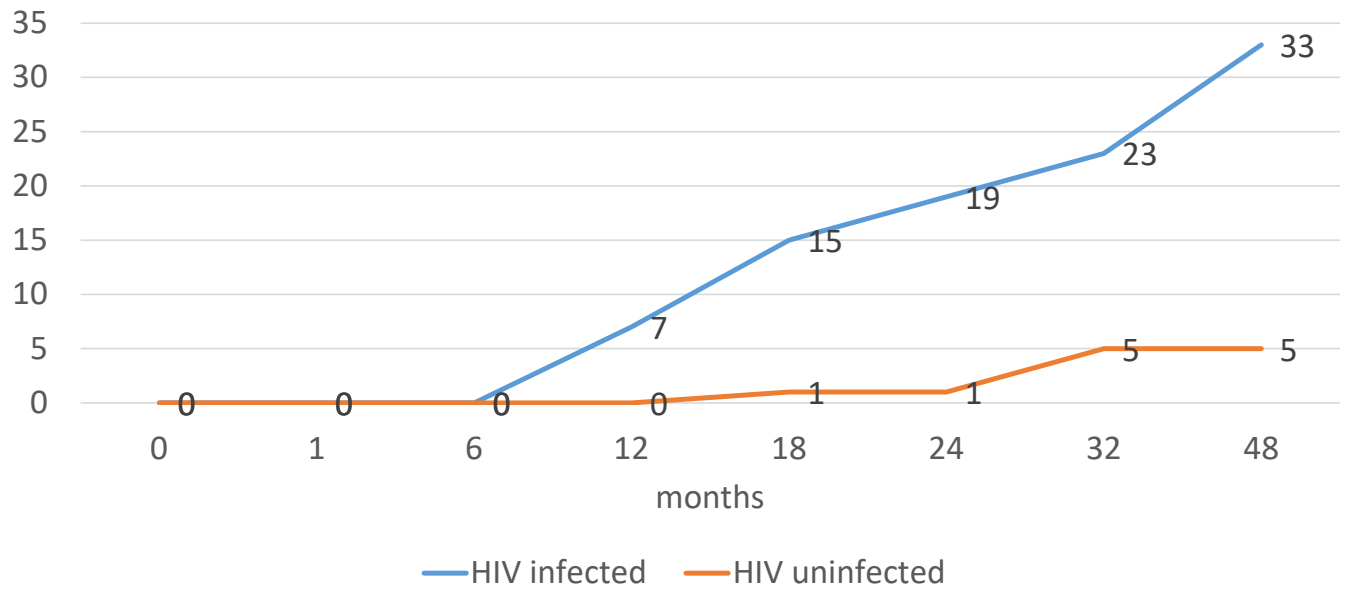
- Parenchymal consolidation (focal or diffuse) ≥ 3 months
- Nodular densities ≥ 3months
- Increased bronchovascular markings or reticular densities ≥ 6 months

Clinical Correlates of Chronic Radiographic Changes (n=83)

- Finger clubbing
- Crackles
- Low oxygen saturation
- 5 with chronic parenchymal consolidation had PJP
- 2 with tuberculosis (one - parenchymal consolidation, one – nodular densities)

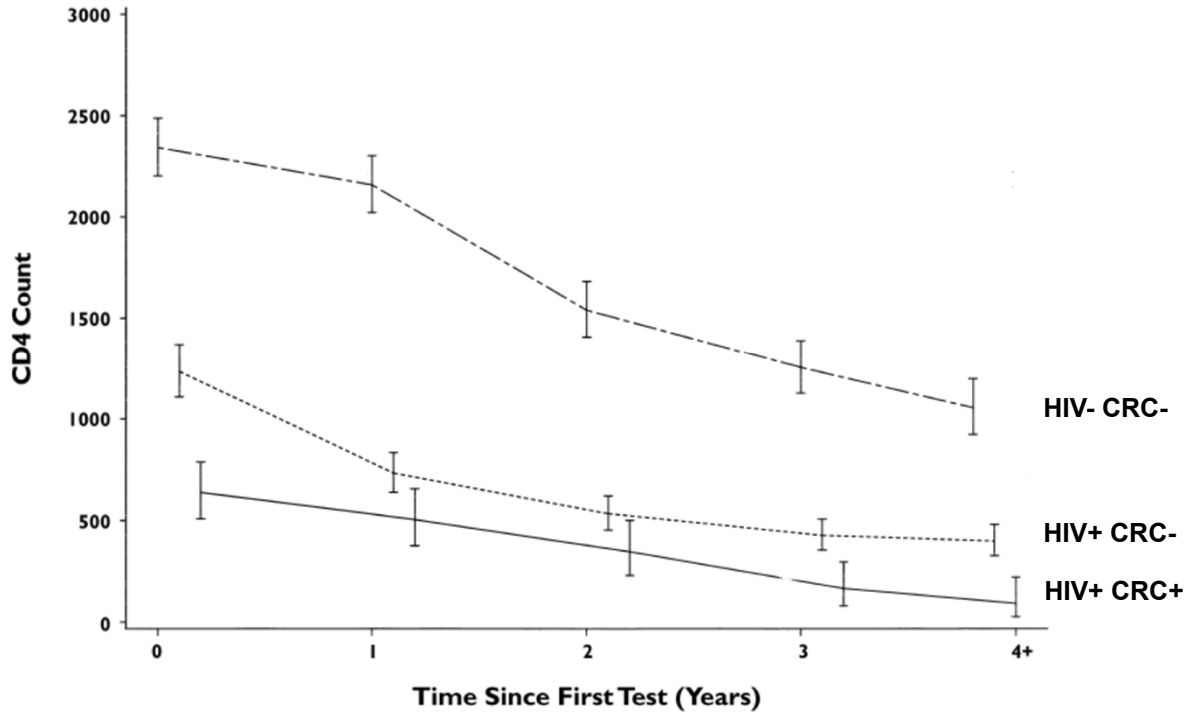
Norton K et al. AJR 2001;176:1553-8

Cumulative Incidence of Chronic Radiographic Changes



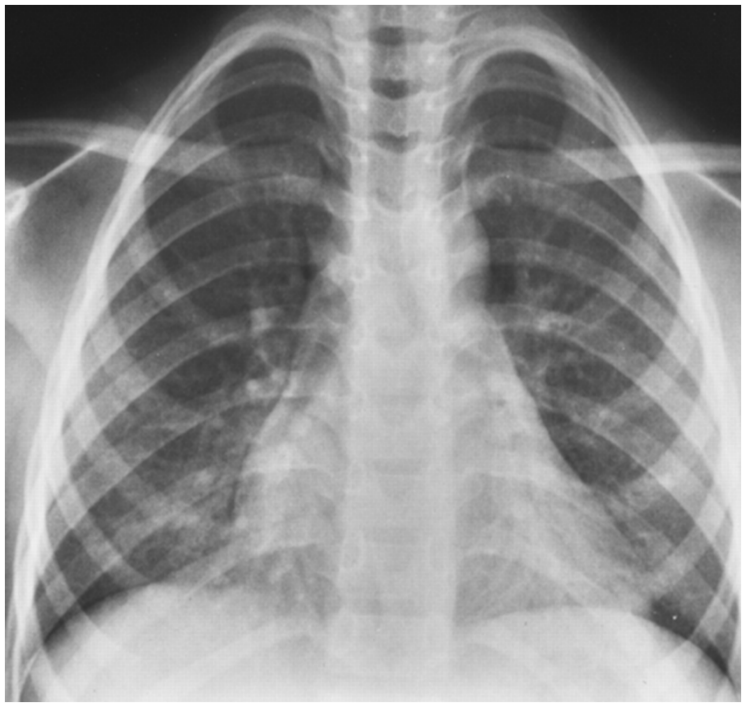
Norton K et al. AJR 2001;176:1553-8

Chronic Radiographic Changes and CD4 Cells

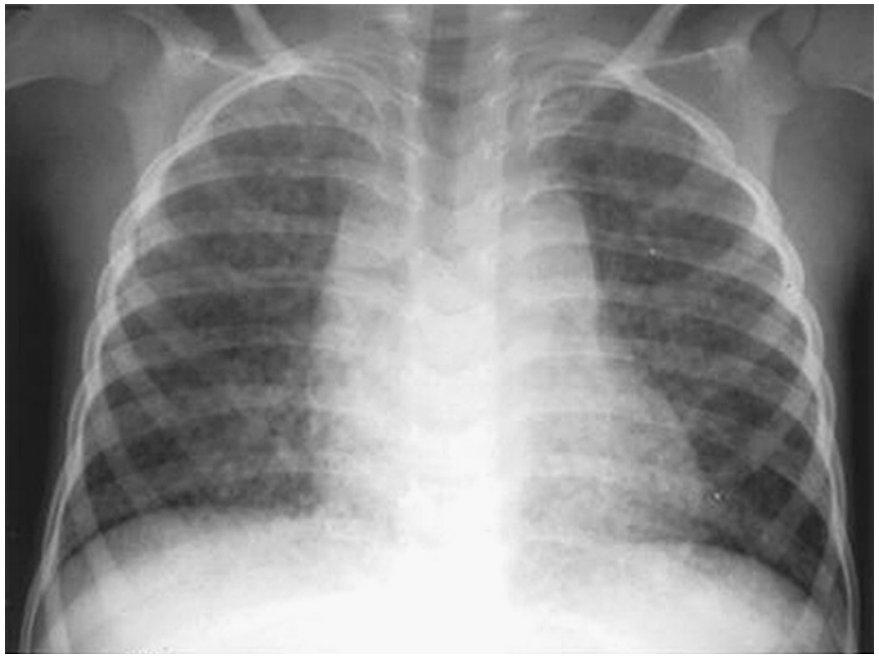


Norton K et al. AJR 2001;176:1553-8

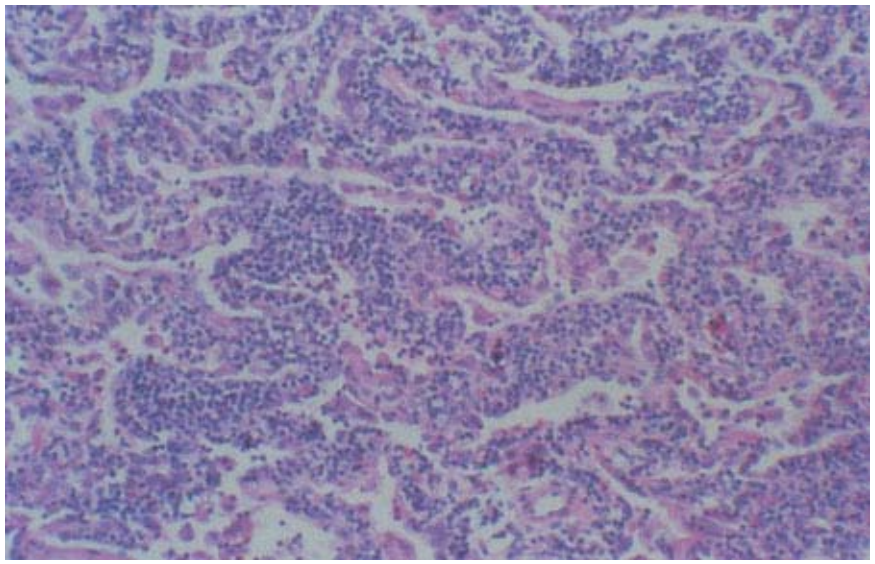
Chronic Infiltrates



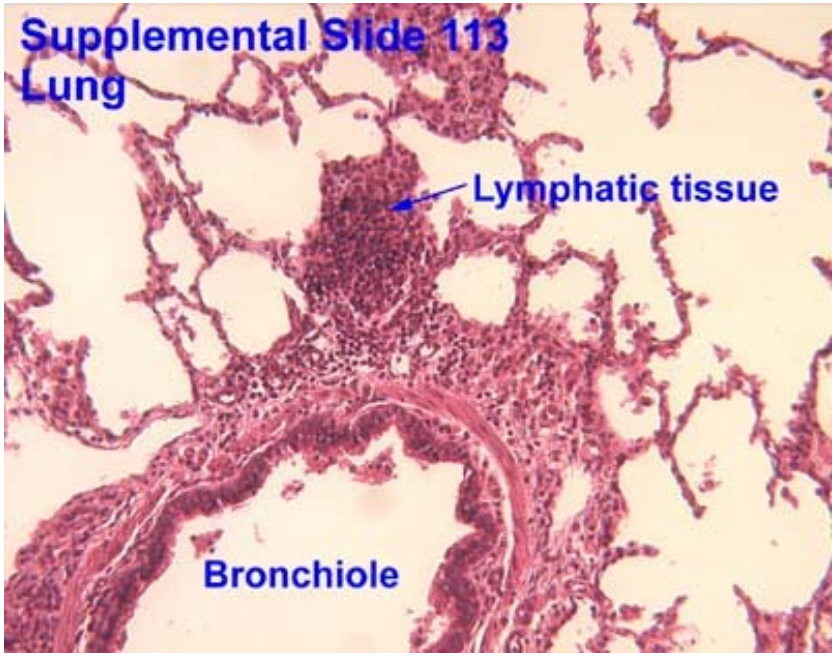
Lymphoid Interstitial Pneumonia



LIP



Bronchial-Associated Lymphoid Tissue (BALT)



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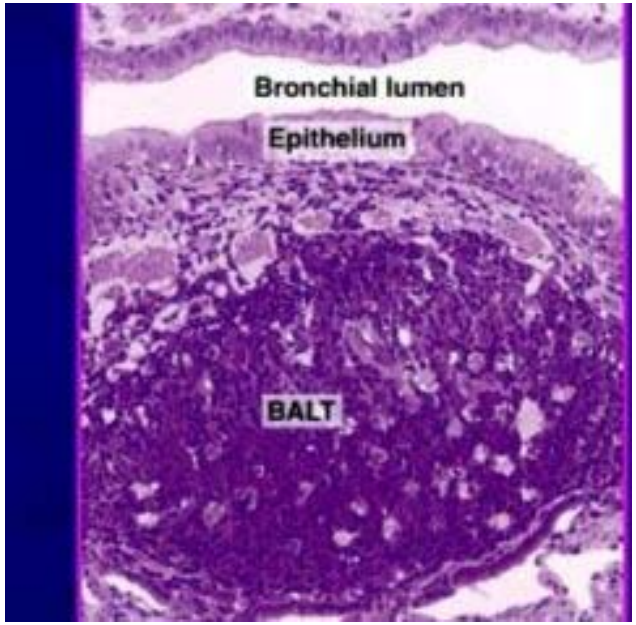


Post Transplant Lymphoproliferative Disorder (PTLD)

- Seen following solid organ transplants and hematopoietic cell transplants
- Related to presence of Epstein-Barr virus (EBV)
- Suspect if elevated EBV viral load

Malignancy in HIV and Immunodeficiency Diseases

- In HIV infected patients EBV infection is associated with non-Hodgkin lymphoma (most common in USA) and smooth muscle tumors (leiomyosarcoma)
- Kaposi's sarcoma is associated with human herpesvirus 8 – (most common in Africa)

Bronchiectasis

- 31/258 (12%) developed bronchiectasis
- 15% of children with LIP developed bronchiectasis at median of 12 months after development of LIP
- 21% of patients developed bronchiectasis at median of 6 months after tuberculosis diagnosis

Pitcher RD et al. Thorax 2015;70:840-846

Lung Function in Perinatally HIV Infected Adolescents on Antiretroviral Therapy

	HIV infected (N=499) Mean ± SD	HIV uninfected (N=106) Mean ± SD	P value
Age (Years)	12±1.6	11.8±1.8	0.355
FVC (% predicted)	87±16	90±13	0.071
FEV1 (% predicted)	87±17	94±13	<0.001
% of children with FEV1 below LLN	27	12	0.001
FEV1/FVC	89±8.7	93±6.3	<0.001
DLCO mlCO/min/mmHg	16.6±3.4	18.1±4.2	0.002

Githinji L et al Annals ATS 2017;14:722

Lung Function in Adolescents with Perinatal HIV Infection vs. HIV Exposed Uninfected

	HIV infected (N=218) Median (Q1,Q3)	HIV exposed uninfected (N=152) Median (Q1,Q3)	
Age (Years)	17.0 (14.3,19.1)	14.7 (12.8,16.6)	<0.01
FVC % predicted	101 (89,111)	99.9 (88, 110)	0.33
FEV1 % predicted	98 (85,109)	97 (84,107)	0.44
Obstructive pattern	24%	24%	
Bronchodilator reversibility	9%	17%	0.052

Shearer W et al. J Allergy Clin Immunol 2017;140:1101

Fixed Airway Obstruction in HIV

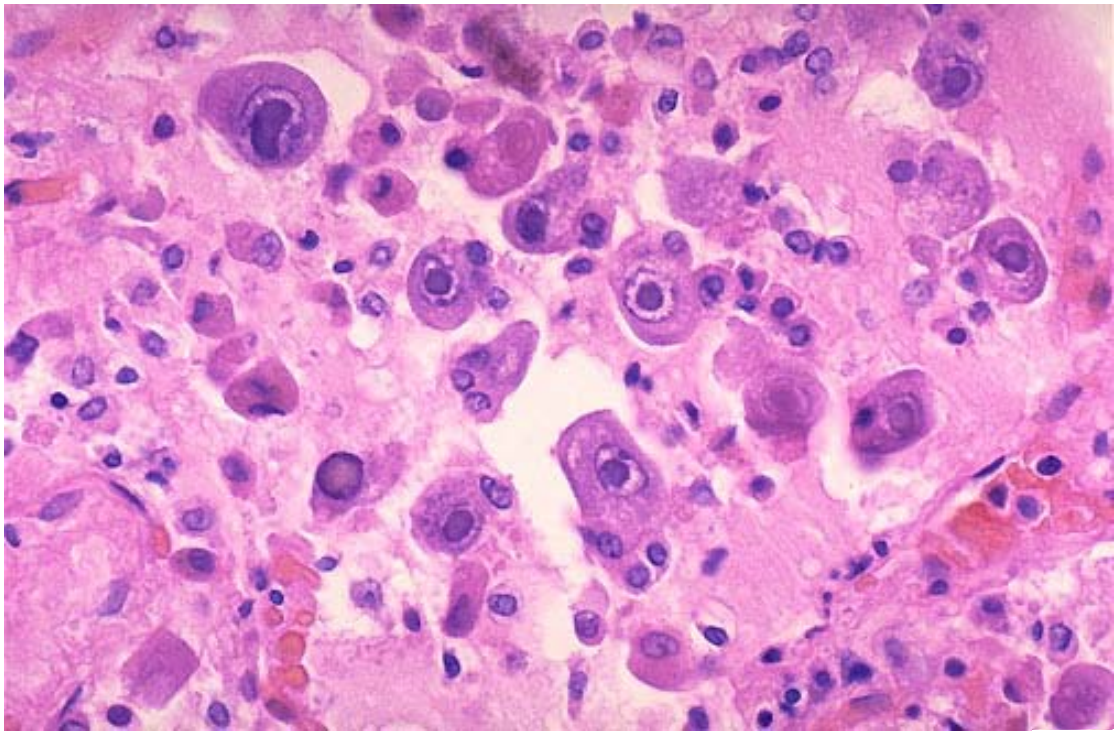
- Prior infections
- HIV associated inflammation and immune dysregulation
- Non-infectious pulmonary complications
- Fibrosis/Bronchiolitis obliterans

Research Questions

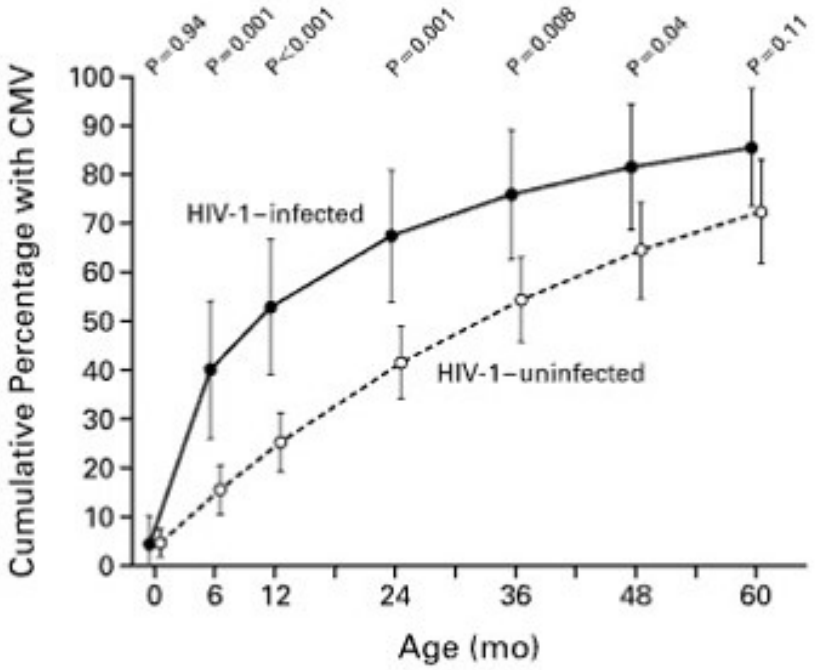
- Is airway obstruction in HIV-infected adolescents a precursor to COPD?
- Does HIV exposure *in utero* affect lung growth and development in uninfected infants?
- What is the long term clinical outcome of HIV-exposed uninfected children?
- What models are best to improve early access to HAART in resource-poor countries?

What roles do CMV, non-tuberculous Mycobacteria and fungi play in HIV and other immunodeficiency diseases?

Cytomegalovirus



Cytomegalovirus Infection



Kovacs A et al. N Engl J Med 1999;341:77-84

Non-Tuberculous Mycobacteria and CMV

- Isolated pulmonary disease with NTM or CMV is uncommon in HIV infection
- May be markers for severe immunosuppression

CMV in BAL Does Not Usually Indicate Clinical Disease

- 34 BAL specimens positive for CMV in 29 patients <19 years
- 12 had associated transbronchial biopsies - none of which confirmed CMV infection
- 79% not treated
- 47% had second pathogen detected in BAL, 9% had rejection
- Probable CMV in only one patient

Burgener EB et al Pediatr Pulmonol 2017;52:112

Case Report

- 15 year old male with history of allogeneic bone marrow transplant
- 3-week history of cough
- CT scan shows bilateral nodular lesions

Serum galactomannan negative
BAL galactomannan positive
Fungal culture from BAL *Aspergillus fumigatus*

How would you interpret results?

A) Proven invasive pulmonary aspergillosis

B) Probable invasive pulmonary aspergillosis

C) Does not meet criteria for invasive pulmonary aspergillosis

D) Results reflect colonization

Answer

B) Probable invasive pulmonary aspergillosis

How would you interpret results?

- Proven invasive pulmonary aspergillosis
- Probable invasive pulmonary aspergillosis
- Does not meet criteria for invasive pulmonary aspergillosis
- Results reflect colonization

Invasive Pulmonary Aspergillosis

- Risk factors
  - Hematopoietic or solid organ transplant
  - High dose corticosteroids
  - Neutropenia
- CT scan shows well circumscribed nodular lesions

Clinical Trials in Organ Transplants

- 59 pediatric lung transplant patients
- 13 (17%) pulmonary fungal infections -3 proven
- Aspergillus, candida, penicillium

Case Report

10 year old girl with lingering cough with colds and otorrhea since 2 years of age. Diagnosed with asthma at 6 years and treated with inhaled corticosteroids and improved. Remained off medications despite recurrence of chronic cough. Developed thrombocytopenia and splenomegaly at 7 years. Treated with corticosteroids for ITP. At 10 years had chronic cough and crackles. CXR showed bilateral patchy infiltrates, atelectasis and probable bronchiectasis.

IgA – 11 mg/dL ↓
IgG – 485 mg/dL ↓
IgM – 89 mg/dL

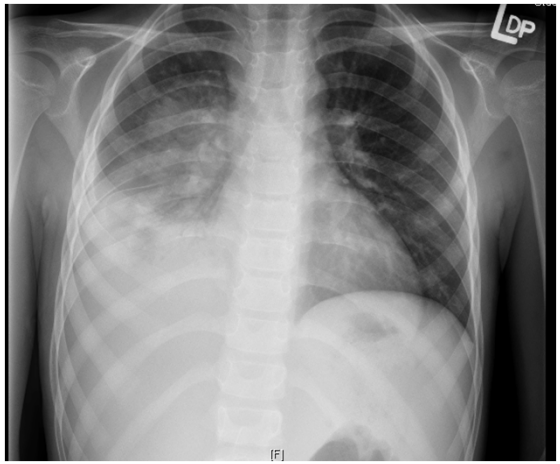
Tetanus, measles, mumps, varicella antibodies negative

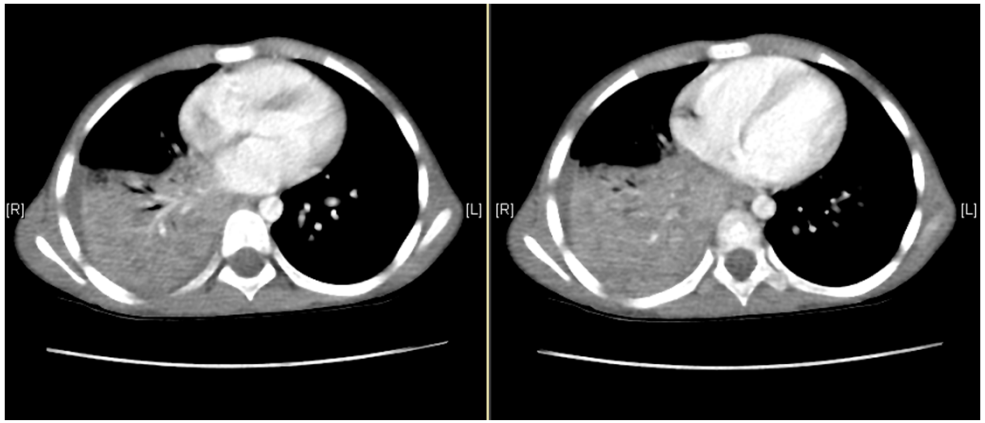
Common Variable Immunodeficiency (CVID)

- Most common severe form of antibody deficiency syndrome (prevalence 1:25,000)
- Age of presentation peaks in 20's to 30s, but can present in early childhood
- **3 characteristics :**
  - Infections
  - Autoimmune diseases, inflammatory lung/GI
  - Malignancy
- **Diagnostic labs:**
  - Low IgG and low IgA and/or IgM
  - Impaired antibody response to specific antigens (vaccines)

Case Report

7 year old boy with no history of recurrent infections treated for pneumonia with effusion with intravenous antibiotics for 2 weeks and chest tube for 5 days. He was readmitted one week later due to persistent fever and cough after 2 week IV treatment for necrotizing right lower lobe pneumonia





Case Report

CBC – WNL
Quantitative immunoglobulins – WNL
Lymphocyte subsets – WNL
Sweat chloride normal

BAL – *Burkholderia cepacia*

What is the most likely diagnosis?

A) primary ciliary dyskinesia

B) chronic granulomatous disease

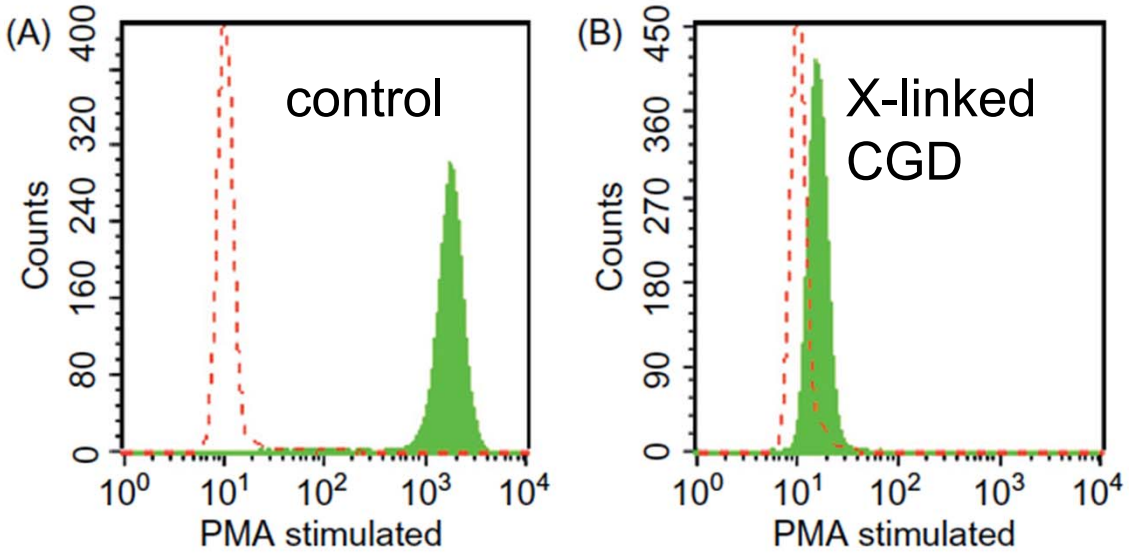
C) ataxia telengectasia

D) Wiskott-Aldrich syndrome

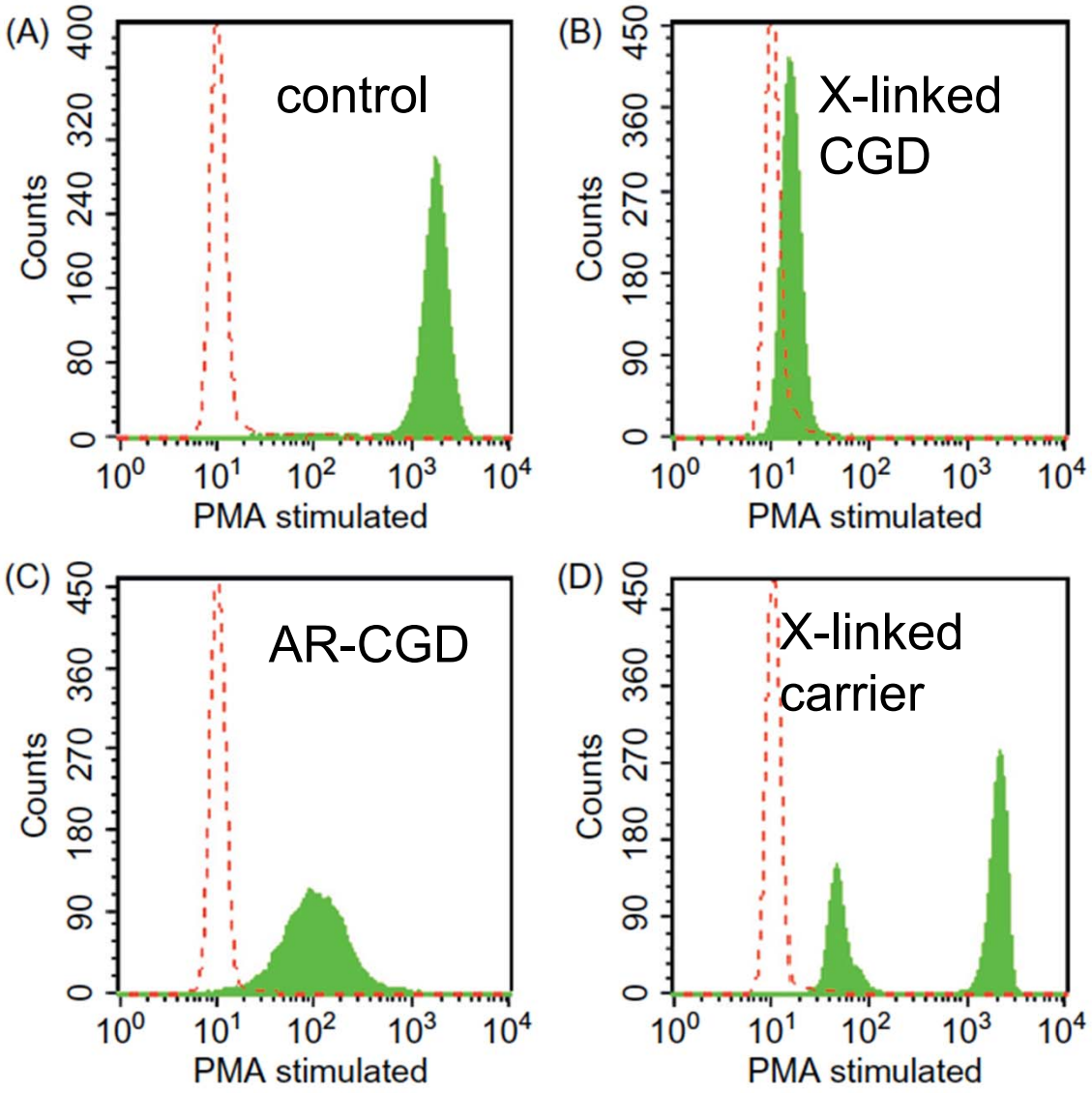
E) combined variable immunodeficiency

Answer

B) chronic granulomatous disease



Dihydrorhodamine (DHR) Assay


(A)
control
Counts
PMA stimulated
(B)
X-linked
CGD
Counts
PMA stimulated
(C)
AR-CGD
Counts
PMA stimulated
(D)
X-linked
carrier
Counts
PMA stimulated

Chronic Granulomatous Disease

- Defective phagocyte NADPH oxidase (phox) enzyme – resulting in failure in intracellular killing
- Increased susceptibility to bacterial and fungal infections
- X-linked (70%), AR (30%)

Genetic Diseases Associated with Immunodeficiencies

- Down Syndrome
  - More frequent and prolonged respiratory infections
- Di George syndrome
- Ataxia Telangectasia (cellular and humoral defects)
  - Recurrent sinopulmonary infections, bronchiectasis, interstitial fibrosis
- Wiskott-Aldrich syndrome (B-cell, T-cell, NK cell abnormalities)
  - Recurrent otitis, sinusitis or pneumonia

Approach to the Child with Suspected Immunodeficiency

- CBC with differential
- Immunoglobulins
- Antibody response (pneumococcus, tetanus, diphtheria)

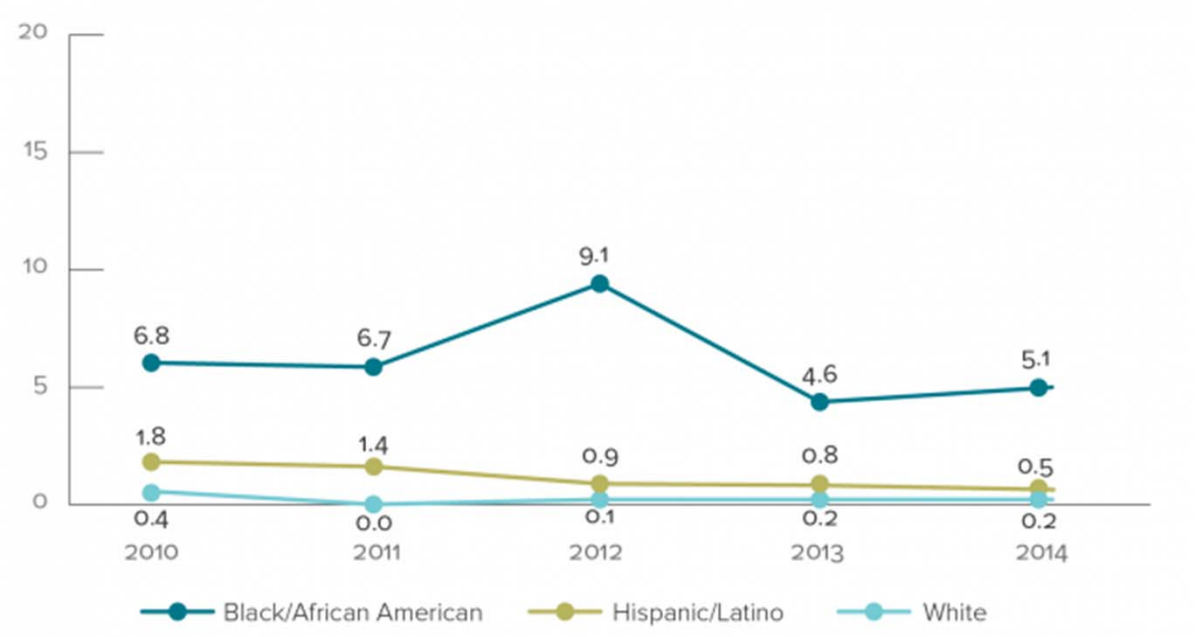
Consider:

- Immunophenotyping of B cell by flow cytometry (number of B cells)
- Genetic testing
- HIV

Evaluation of Immunocompromised Host with Respiratory Symptoms

- Chest x-ray; Chest CT scan
- Induced sputum
- Bronchoscopy with BAL
- Percutaneous needle biopsy, transbronchial biopsy, VATS, open lung biopsy
- Nasal swab
- Blood culture
- Urinary antigen tests

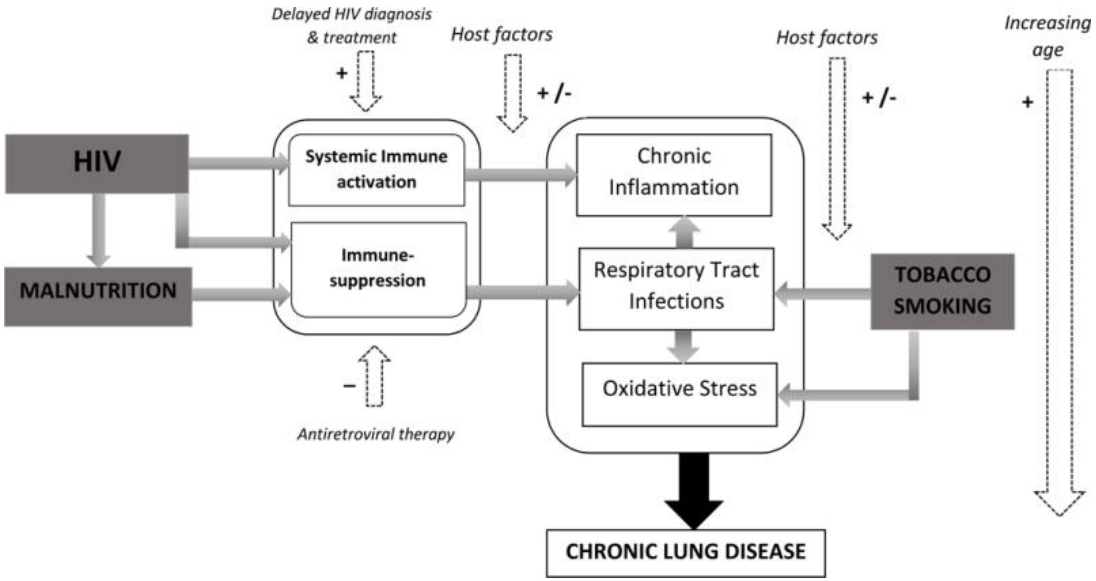
Rates of Perinatally Acquired HIV Infections in USA



HIV in USA

- In 2016, 2225 children <13 years were living with perinatally acquired HIV
- Of persons living with HIV in 2016, 5304 were aged 13-19

Pathogenesis of CLD in HIV



Attia EF et al. Curr Opin Infecct Dis 2017;30:21

HIV-Exposed and Uninfected Children

- Increased risk of pneumonia?
  - Pneumonia incidence ratio 1.62 in HIV-exposed*
- Immune dysregulation?

*Le Roux DM et al. Lancet Global Health 2015;3:e95-103