Discovery of HIV and Early Findings
2/26/13

Jay A. Levy, M.D.

BIOGRAPHY:

Dr. Jay A. Levy is Professor of Medicine in the Division of Hematology/Oncology, Research Associate in the Cancer Research Institute and the Director of the Laboratory for Tumor and AIDS Virus Research at the University of California in San Francisco (UCSF). He obtained his M.D. degree from Columbia University, New York after receiving his B.A. from Wesleyan University in Connecticut and joined the Department of Medicine and the Cancer Research Institute at UCSF in 1972. Dr. Levy co-discovered HIV in 1983 and during the last 30 years, he and his research group have dedicated their efforts to biologic, immunologic, and molecular studies of the AIDS virus. His pioneer studies on heat inactivation of HIV in clotting factor preparations has protected many hemophiliacs from HIV. He also discovered a novel immune response that controls HIV infection through the production by CD8+ lymphocytes of a newly identified antiviral factor, CAF. Dr. Levy is a Fellow of the American Academy of Arts and Sciences, American Association for the Advancement of Science, and the American Academy of Microbiology. Among his honors are: Award of Distinction from the American Foundation for AIDS Research (AmFAR); Honorary Degree in Science from Wesleyan University; selection by the San Francisco Examiner as one of the ten most influential people in the San Francisco Bay Area; 45th Faculty Research Lecturer at UCSF; the Abbott Laboratories Award for outstanding immunology research; and the Gold Medal for excellence in medical research from Columbia University. Dr. Levy is the Editor-in-Chief of the highly-cited journal AIDS and has published over 600 scientific articles and reviews and fourteen books dealing with viruses, immunology and infectious diseases.

BIBLIOGRAPHY:


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Major Epidemics of the World
- Bubonic Plague
- Cholera
- Dengue
- Diphtheria
- Influenza
- Malaria
- Measles
- Mumps
- Schistosomiasis
- Smallpox
- Syphilis
- Tuberculosis
- Typhus
- Yellow Fever

Factors Condusive to the Emergence of the AIDS Epidemic
- Migration of carriers into cities - increased interpersonal contacts
- Poverty; prostitution
- International travel
- Sexual behavior
- IV drug use
- Receipt of blood and blood products

How Does HIV Differ from Other Epidemic Pathogens?
- Directly attacks the immune system
- Involves virus incorporation into the cellular genome
- Establishes a chronic infection before becoming pathogenic
- Involves an agent that frequently changes or modulates itself within the host.
- Can recruit other cells by direct infection or cell:cell transfer

Seven Deadly Symptoms
- Fever, not explained, weight loss of ten pounds or more over a period of time
- Persistent unexplained malaise for more than 3 months
- Persistent unexplained diarrhea for more than 3 months
- Persistent unexplained fatigue that prevents usual activities, for more than 1 month
- Loss of appetite or unexplained weight loss of 10 pounds in a month
- Lesion on mouth or unusual sore
- Skin rash, unusual or unexplained
- Vision problems, unusual or unexplained
Pneumocystis jiroveci pneumonia

HHV-8

Hairy leukoplakia provided by J. Greenspan, UCSF
**AIDS-Associated Retrovirus (ARV)**

**LAV / HTLV III / ARV**

ARV = HIV-1_{SF}

**Human Immunodeficiency Virus (HIV)**

**Components of HIV Infection**
**HIV Pathogenesis**

**Virus : Host Interactions**

**HIV: Cell Entry**

**HIV Biologic Diversity**

**Coreceptor Usage by HIV-1**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Tropism</th>
<th>Coreceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSI*</td>
<td>Macrophage</td>
<td>CCR-3</td>
</tr>
<tr>
<td>SI</td>
<td>T-cell line</td>
<td>CXCR-4</td>
</tr>
<tr>
<td>SI</td>
<td>Dual</td>
<td>CXCR-4, CCR-5, CCR-2b</td>
</tr>
</tbody>
</table>

* Also non-macrophage-trophic NSI Strains

**Initial HIV Infection**
HIV and its Diseases: Case Presentations from the Clinic
2/26/13

C. Bradley Hare, MD

BIOGRAPHY:

C. Bradley Hare, MD is Associate Professor of Clinical Medicine and Medical Director, UCSF HIV/AIDS Division at San Francisco General Hospital. Research Interests: Dr. Hare conducts patient-based research on a variety of topics important to HIV clinical management, the inspiration for which comes directly from observations in the clinic. Current areas of focus include HIV and Hepatitis C Virus (HCV) co-infection, where he studies the epidemiology, natural history and treatment of acute hepatitis C infection, the use of novel agents in the treatment of HIV-HCV co-infection, and models of HCV treatment in primary care settings. He also conducts research on HIV testing in medical settings such as the Emergency Department, linkage to care after HIV testing, and implementation of a patient-centered medical home for people aging with HIV infection.
HIV and Its Diseases: Case Presentations from the Clinic

Brad Hare, MD
Associate Professor of Clinical Medicine
Medical Director, HIV/AIDS Division
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February 26, 2013

Common Infections in HIV

- Bacterial Infections
  - Tuberculosis
  - Mycobacterium avium (MAC)
  - Bartonella
- Fungal Infections
  - Oral Candidiasis (Thrush)
  - Pneumocystis (PCP)
  - Cryptococcus
- Sexually Transmitted Infections (STIs)
- Viral Infections
  - Cytomegalovirus (CMV)
  - Varicella Zoster Virus (VZV; shingles)
  - Progressive Multifocal Leuкоencephalopathy (PML)
  - HHV-8 (Kaposi’s Sarcoma)
- Parasitic Infections
  - Toxoplasmosis

Case 1

- 24yo gay man with newly diagnosed HIV infection here for his first visit
  - Got tested because he started losing weight and noticed white patches in his mouth

Oral Candidiasis (Thrush)

- Epidemiology
  - Ubiquitous fungus on skin and mucosal surfaces
  - More common in setting of low CD4 or antibiotic use
- Clinical Presentation
  - White plaques on any mucosal surface can be wiped off, leaving erythematous base
  - In more severe infection, can involve the esophagus causing pain on swallowing
- Diagnosis
  - Clinical + KOH prep of scraping or culture
Oral Candidiasis (Thrush)

- Treatment
  - Topical antifungals – lozenges, liquids
  - Oral antifungals
    - Fluconazole 200 mg once daily

Case 2

- 53yo WM with AIDS (CD4 = 24; VL >500,000)
  - Previously declined antiretrovirals or prophylaxis
  - Started on antiretroviral therapy 4 months ago
  - 2 months ago: CD4 = 123; VL = 1,280
  - For the last 2 days, he has had a very painful rash that started on right shoulder and has been spreading on chest and neck. Unable to sleep because the sheets hurt to touch his skin. No fevers.

Varicella virus (VZV) – Shingles

- Epidemiology
  - Reactivation of latent VZV from dorsal root ganglion of the spinal cord
  - 15-25x more common in HIV+
- Clinical Presentation
  - Grouped vesicles on erythematous base
  - Follows a dermatome
  - Often multi-dermatomal or disseminated in HIV positive
  - Post-herpetic neuralgia

Case 3

- 34yo woman with AIDS (CD4 = 4)
  - Not taking her antiretroviral medications
  - Complains of 2 weeks of seeing ‘floaters’
  - You send her emergently to ophthalmology clinic …

Varicella virus (VZV)

- Diagnosis
  - Clinical; Culture or identify virus in lesion
- Treatment
  - Antivirals: Acyclovir or Valacyclovir or Famciclovir
    - Intravenous if severe; oral OK otherwise
  - Treatment must be begun with 72h of onset of vesicles for any benefit
- Prevention
  - Studies ongoing of Varicella vaccine in HIV positive
Our patient                              Normal

Cytomegalovirus (CMV)
• Epidemiology
  • Very common – acquired through sexual or intimate contact
  • 85% Seropositivity in sexually active gay men, 60% in heterosexual populations
• Clinical Presentation
  • ‘Floaters,’ vision changes, decreased visual acuity, blindness
  • CMV can also cause ulcers in the esophagus or colon, diseases of the brain and nervous system, pneumonia, liver infection

Cytomegalovirus (CMV)
• Diagnosis
  • CMV antibody blood test indicates prior infection
  • Ophthalmologic exam with large creamy, white area with granular borders and perivascular exudates and hemorrhages
  • Starts in periphery and moves toward macula or optic disc
• Treatment
  • Intravenous or oral antivirals – ganciclovir, valganciclovir, foscarnet
  • Ocular implant that releases ganciclovir

Case 4
• 57yo man who has been HIV-positive for 25 years
• Taken many antiretroviral medications over the years
• Currently with CD4 = 326 and HIV viral load undetectable
• “My face and legs are too skinny.”

HIV Lipodystrophy
**Lipodystrophy**

- Changes in body fat
  - Decreases in fat in face, limbs, buttocks
  - Increases in fat on back of neck ("buffalo hump"), breasts, intra-abdominal
- Related to use of certain older HIV medications as well as HIV itself and some genetic factors
- Treatment
  - Remove offending medications
  - Facial填者
  - Surgery

**Case 5**

- 57yo man with HIV infection for 22 years
- Current CD4 = 448; HIV viral load undetectable on antiretroviral medications
- Also has mild high blood pressure and mildly elevated cholesterol
- Developed sudden onset of chest pain and was found to have a myocardial infarction
- On catheterization, he had severe blockages in multiple coronary arteries, requiring placement of two stents

**HIV and Aging**

- By 2015, over 50% of all people living with HIV will be at least 50 years old
- Indications from clinical and laboratory studies that HIV may be leading to “premature aging”
  - Conditions that typically show up later in life – such as heart disease, cancers, cognitive decline, osteoporosis – are seen earlier among people living with HIV
- Area of active research

**Case 6**

- 38yo gay man with HIV (CD4 = 328; HIV Viral load undetectable) on stable antiretroviral medications
- Moved to SF 9 months ago from LA
- Treated for rectal gonorrhea 3 months ago
- On routine labs, his liver enzymes are noted to be markedly elevated (ALT = 1105; AST = 1194)
- He feels fine and denies any new medications, herbs or supplements

**Case 6**

- He is tested for hepatitis, syphilis, mononucleosis
- Results return positive for new hepatitis C infection

**Hepatitis C Virus (HCV)**

- 30% of people with HIV also have HCV
  - Common routes of exposure
- Increasing numbers of new cases of HCV from sex, primarily among HIV-positive men who have sex with men
  - Risk factors include traumatic anal receptive sex
  - 20-25% of HCV infection may spontaneously clear without treatment
  - Treatment during the acute phase of infection is particularly effective
Case 7

- 33yo man hospitalized for HIV and treatment of tuberculosis
- Noticed 3-4 painless, red skin lesions on his chest and arm over the last month

Bartonella – Bacillary Angiomatosis

- Epidemiology
  - Common in kittens; from fleas on cats
- Clinical Presentation
  - Friable vascular papules, plaques and nodules; often tender; surrounding erythema
- Diagnosis
  - Major differential diagnosis is Kaposi’s Sarcoma
  - Skin biopsy is test of choice
  - Culture and blood tests for antibodies can also be helpful

Bartonella

- Treatment
  - Oral antibiotics for a prolonged course
- Prevention/Prophylaxis
  - Careful flea control of cats; wash after handling cats and especially kittens
  - Bartonella species also cause other diseases such as Cat Scratch Fever, Trench Fever, peliosis hepatitis, endocarditis

Kaposi’s Sarcoma

- Tumor of the skin, oral cavity, gastrointestinal tract or lungs
- Caused by Human Herpes Virus 8 (HHV-8)
  - aka Kaposi’s Sarcoma Herpes Virus (KSHV)
  - Transmitted through saliva
- Treatment
  - First line treatment is treating HIV with antiretroviral medications
  - Radiation or chemotherapy used for more severe or widespread disease
Case 8

- 37yo man with HIV/AIDS (CD4 = 120, 1 year ago)
- Came to the ED with 3 weeks of dry cough, shortness of breath, night sweats
- Vital signs show low grade fever and low oxygen levels in his blood

Pneumocystis pneumonia

- Caused by *Pneumocystis jirovecii*
  - Human-specific yeast-like fungus
  - Found on all continents except Antarctica
  - 75% of children test positive for it by age 4
- Diagnosis
  - Characteristic presentation, X-rays and CT scans
  - Most often when CD4 <200
  - Identify the organism in samples from induced sputum or broncoalveolar lavage

Pneumocystis pneumonia

- Treatment
  - Antibiotics (trimethoprim–sulfamethoxazole, clindamycin + primaquine, pentamidine, or atoviquone) for 21 days in combination with glucocorticoid steroids (prednisone) to reduce lung inflammation
- Prevention
  - Give prophylactic antibiotics to all HIV-infected people with CD4 <200

Case 9

- 45yo man with advanced AIDS, visual changes and personality changes
Progressive Multifocal Leukoencephalopathy (PML)

• Causative Organism
  • JC Virus

• Epidemiology
  • CD4 usually < 100

• Clinical Presentation
  • Develops insidiously with single focus at first (limb weakness, poor balance, visual defects, altered level of consciousness)
  • Progresses to multiple deficits
  • Seizures in up to 20%
  • Alertness is preserved until late in the course

Case 10

• 29yo transgender female with CD4 = 120 and headache for 2 weeks

Cryptococcal Meningitis

• Causative Organism
  • Cryptococcus neoformans or C. gattii

• Epidemiology
  • Common environmental fungus – pigeon droppings
  • CD4 usually < 100

• Clinical Presentation
  • Meningitis: Slowly progressive headache, stiff neck (25%), focal findings (20%), nausea/vomiting
  • 20-60% have extraneural disease (skin, bone)
  • Cryptococcemia: Fatigue, fever, pulmonary symptoms
Cryptococcal Meningitis

- Diagnosis
  - Culture organism in spinal fluid
  - Antigen test in blood or spinal fluid is very sensitive and specific
- Treatment
  - Intravenous and oral antifungals
    - Amphotericin + flucytosine, followed by fluconazole
  - Repeat spinal taps to lower increased intracranial pressure, if elevated

Case 11

- 27yo man with CD4 = 30 and not taking any medications
- Admitted to the hospital with a seizure

Toxoplasma Encephalitis

- Causative Organism
  - *Toxoplasma gondii* (parasite)
- Clinical Presentation
  - Altered mental status (70%); focal neurologic deficit (60%); headaches (50%); seizures (30%)
  - Fever, confusion, coma
  - Symptoms occur over days
- Diagnosis
  - Brain biopsy is gold standard, but rarely done
  - Characteristic MRI; positive blood test indicating prior exposure to Toxoplasma

Case 12

- 48yo man initiated antiretrovirals 6 months ago, when CD4 = 57; HIV viral load >500,000
- Now has 2 weeks of enlarging neck mass, pain
  - CD4 = 122; HIV viral load = 1,200
- Admitted to the hospital for evaluation, including CT scan and biopsy

Toxoplasma Encephalitis

- Treatment
  - Oral antibiotics – pyramethamine + sulfadizine + leucovorin
- Prevention
  - Avoid eating undercooked meat; wash hands after cooking and gardening; wash hands after changing cat litter box; avoid stray cats; feed cats only dried or canned food
  - If blood test indicates prior exposure, give prophylactic antibiotics when CD4 <100
Diagnosis: Mycobacterial infection with immune reconstitution

Mycobacterium avium complex (MAC)

- Epidemiology
  - Organism ubiquitous in soil, food, water
  - CD4 < 50
- Clinical Presentation
  - Disseminated infection with fever, weight loss, night sweats, diarrhea, abdominal pain, anemia, neutropenia
  - Enlarged, tender lymph nodes
- Diagnosis
  - Blood culture, bone marrow or lymph node culture

Mycobacterium avium (MAC)

- Treatment
  - Combination oral antibiotics
    - Clarithromycin + ethambutol +/- rifampin
- Prevention
  - Prophylactic antibiotics when CD4 <50
    - Azithromycin weekly or clarithromycin

Immune Reconstitution Syndrome (IRIS)

- Vigorous immune response to pathogens after initiation of antiretroviral treatment
- Paradoxically makes symptoms of the infection worse
- Immune system may react to an infection that is already known or unknown
- Treatment consists of continuing antiretroviral medications and adding steroids

Summary

- When managing an HIV-infected patient, the degree of immunosuppression is a big clue to what conditions to look for
- Opportunistic infections are still seen today, but our goal is to diagnose patients early and engage people in care so they can start treatment and prevent these illnesses from occurring
- People with HIV can also get the same illnesses that people without HIV do, and some of those may be happening more often and at younger ages