

## HIV-1 Infection: a case oriented approach to some old problems



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## A typical adolescent

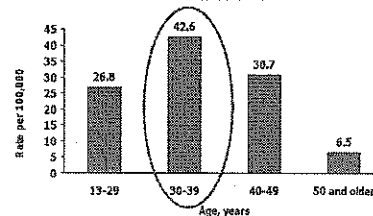
- 17 yo male reveals that he is MSM with *high risk* sexual behavior in past four weeks.
- Reports transient rash, fever, and malaise but no other symptoms.
- PE is normal except for 3-5 cm bilateral inguinal and axillary adenopathy
- He's worried that he may have HIV

## What should you do next?

1. Do a rapid HIV screening test and if negative re-assure him that he's probably not infected.
2. Referring to the county Health Department for anonymous testing.
3. Do a rapid HIV screening test and if negative do an quantitative HIV RNA.
4. Tell him that he needs to tell his parents and get their consent prior to doing HIV screening.

Answer: Do a rapid HIV screening test, if negative do an quantitative HIV RNA.

Estimated rates of new HIV Infections, by age, 2006\*



\*50 States and District of Columbia

Hall, JAMA, 300: 520-529, 2008

## Where were persons tested for HIV?

	2002	2006
Private doctor/HMO	44%	53%
Hospital, ED, Outpatient	22%	18%
Community clinic (public)	9%	9%
HIV counseling/testing	5%	5%
Correctional facility	0.6%	0.4%
STD clinic	0.1%	0.1%
Drug treatment clinic	0.7%	0.4%



2006 National Health Interview Survey



Branson, Natl HIV Summit Nov 2008

## CDC HIV Testing Recommendations

- HIV screening recommended for all patients aged 13-64 in all health-care settings
- HIV screening should be voluntary
- Opt-out screening: patients are notified that testing will be performed unless they decline
- Separate written consent for HIV testing not recommended; general informed consent is sufficient
- Prevention counseling should not be required
- High-risk patients should be screened at least annually

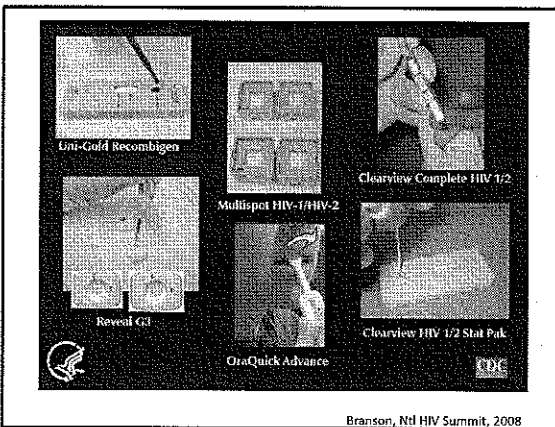
MMWR, Sept 2006

### Florida Law Related to HIV Testing 2008

- **Minors:**
  - Person aged 12 or older do NOT need parental consent to be tested for HIV (FS 381)
  - HIV is considered an STD in Florida (FS 384.3)
- **Pregnant women:**
  - Mandatory offering of HIV testing to pregnant women at first visit and 28-32 weeks
  - Testing is "opt out" meaning no additional consent required (FS 384.31).
- **Adults:**
  - Consent still required, changes are proposed.

### Rapid HIV Tests

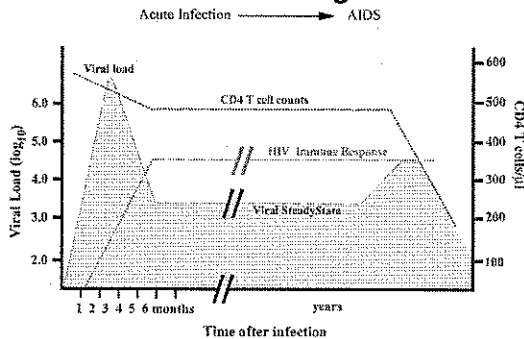
- Rapid HIV Antibody tests are comparable to EIA assays in sensitivity and specificity.
- Results can be available in 20-30 minutes
- Some are CLIA waived for point of care testing
- Confirmation with a Western blot-not an EIA or ELISA
- Used in Labor and Delivery, ER setting and occupational exposures



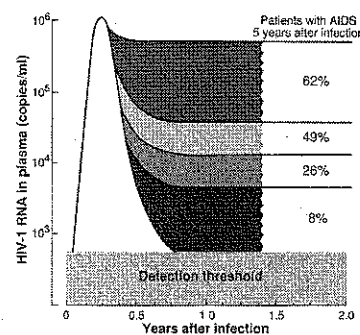
### Current FDA Approved Rapid tests

Test Kit Name	Manufacturer	Specimen Type	CLIA Category	Equipment Required
OraQuick Advance Rapid HIV-1/2 Antibody Test	Orasure	Whole Blood, Oral Fluids	Waived	Timer
		Plasma	Moderate Complexity	
Reveal G3 Rapid HIV-1 Antibody Test	MecMira, Inc	Serum, Plasma	Moderate Complexity	Centrifuge, Refrigerator
Uni-Gold Recombigen HIV Test	TrinityBiotech	Whole Blood	Waived	Timer
		Serum, Plasma	Moderate Complexity	
Multispot HIV-1/HIV-2 RapidTest	BioRad Lab	Serum, Plasma	Moderate Complexity	Centrifuge, Refrigerator, Lab Equipment
Clearview HIV 1/2 Stat Pak	Chembio diagnostics	Whole Blood	Waived	Timer
		Serum, Plasma	Moderate Complexity	
Clearview Complete HIV 1/2	Chembio diagnostics	Whole Blood, Serum, Plasma	Moderate Complexity	Timer

### Clinical Disease Progression



### Steady State Viral Load and Disease Progression

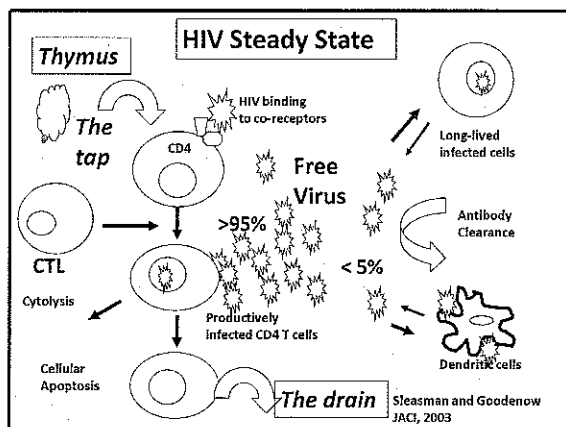


Walker, NEJM, 2002

- Entry via mucosal surfaces.
- Initial infection in DC and macrophages by R5 viral strains.
- Infected APC travel to regional lymph nodes.
- Local viremia by third day of infection.
- Dissemination to organs with acute viremia and illness by second week.

### Testing Algorithm

- Rapid antibody-based test and if positive confirm by blood ELISA and Western Blot.
- If Rapid test is negative, carry out antigen (HIV RNA) based assay
  - Patient may be in acute infection prior to sero-conversion
- Provide counseling regardless of test results
  - Risks for infection
  - Risks for transmission

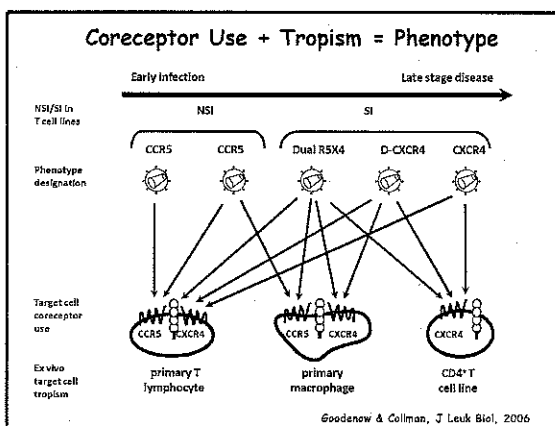


### Clinical Staging of newly identified HIV infection

- Quantitative HIV viral load by PCR
- T cell subset analysis
  - CD4/CD8 ratio and %
  - Absolute CD4 Count
- PPD and CXR
- Determine co-infection status
  - Hepatitis B and C, CMV, EBV, syphilis, Toxo, Crypto, HPV, HHV-6/7, Zoster, MAI,

### Traditional Paradigm of HIV Immune Pathogenesis

- Tap and drain T cell dynamics
- Acute infection characterized by CD8 T cell activation
- Slow/steady depletion of CD4 T cell numbers and function over time
- HAART restores CD4 T cells and corrects immune defects



### CCR5 on T cells

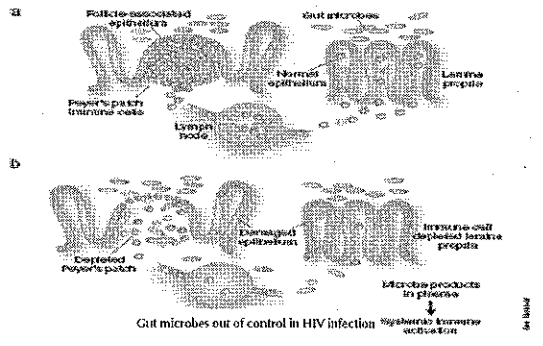
- Predominant CCR5 expression is on Memory blood CD4(CD45RO) T cells and macrophages
- These T cells are preferentially infected and killed by CCR5 tropic viruses
- Infection induces activation of both CD4 and CD8 T cells
- The majority of memory CD4 and CD8 Memory CCR5 T cells are depleted in the GALT

### The tsunami of acute HIV infection

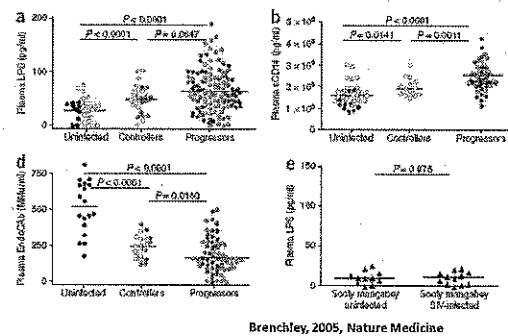
- Between days 7 and 21 post infection 30 – 60% of CD4 CD45RO CCR5 memory T cells become infected.
  - Peyer's patches, Inguinal and mesenteric LN
  - TH17 T cells within the intestinal mucosa
- These cells are never totally replaced.
- T cell counts in the peripheral blood do not reflect the massive loss in the tissues.

Mattapallil, *Nature*, 2005  
Veazey, *Science*, 1998

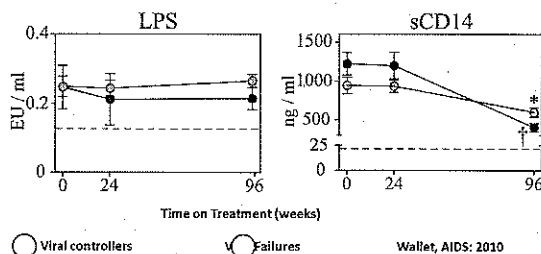
### Consequences of Viral Replication in the GALT



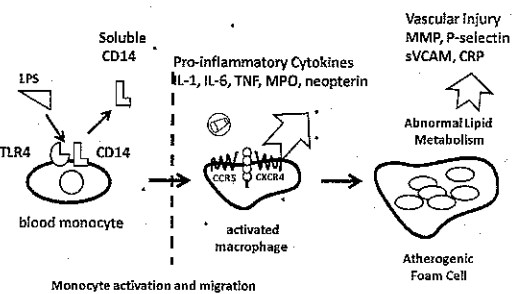
### Evidence of Microbial Translocation



### ART Fails to Reverse Microbial Translocation or Macrophage Activation



### LPS induces activation of monocyte/macrophage



**Should you start treatment?  
Factors to consider**

- Absolute CD4 T cell count
  - CD4 < 350 cell/ $\mu$ L
- Steady state viral load
- Capacity to adhere to therapy
- Co-morbidities
  - Tuberculosis

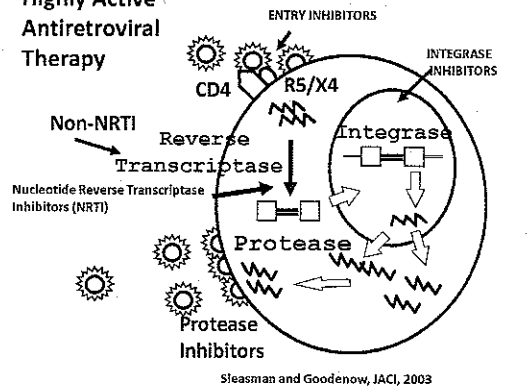
**The HAART ERA**  
Applications of combination Antiretroviral Therapy.



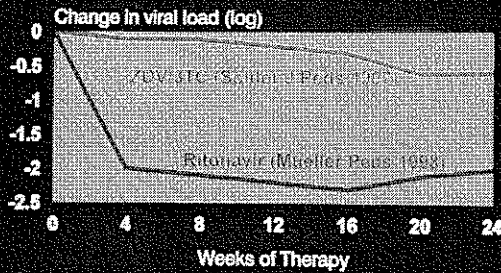
**Which antiretroviral agents?**

- Two nucleotide/nucleoside reverse transcriptase inhibitors plus a highly active anti-retroviral (NNRTI or PI)
- Decision based on:
  - Toxicity profile
  - Cost/availability
  - Adherence
  - Pregnancy

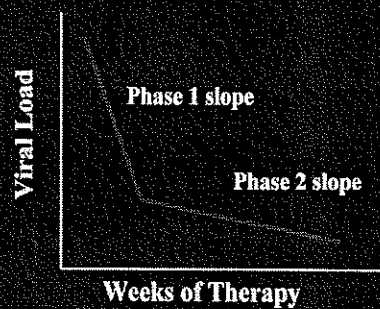
**Highly Active Antiretroviral Therapy**

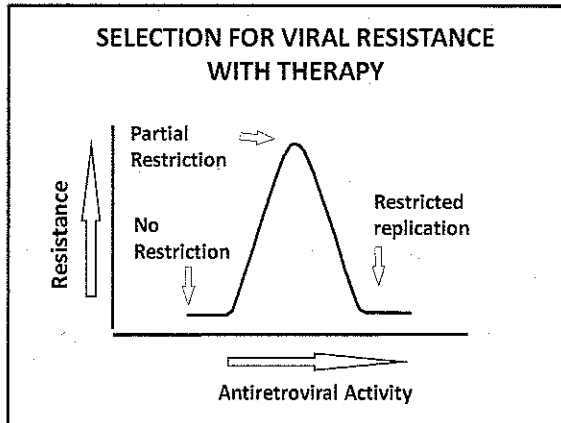


**Changes in viral burden  
NRTI vs Protease inhibitor**



**Change in Viral Load with Therapy**





### Impact of chronic macrophage activation in HIV-infection

- Macrophage activation (sCD14) best predictor of overall mortality in HIV-infected adults (Sandler, *JID*, 2011)
- High levels of LPS and sCD14 correlates with HIV encephalopathy (Acunta *Plos1*, 2008)
- HIV-infected adults have a 3-4 fold high risk of CAD compared to adults with similar risk. (Grunfeld *AIDS* 2009)

### Treatment Decision

- Indirect effects of inflammation on end organ dysfunction
  - (LPS & HIV)
  - HIV associated neurocognitive impairment
  - Atherosclerosis
  - Renal Disease
- Direct effects on HIV on endothelium
- Long term dyslipidemia associated with ART
- Emergence of ART drug resistance

### Case 2: 2:00 am call from L&D

- 25 yo pregnant female at 39 weeks gestation arrives in the ED and is found to be HIV+ based on rapid screening. No prenatal care, no ART
- Based on history, mother is asymptomatic, no other STDs, uneventful pregnancy

### What should you do next?

1. Send a confirmatory HIV Western blot and call back with results.
2. It's too late to do anything for the child, will see in infant in nursery tomorrow.
3. Too late for ART but deliver child by C-section
4. Begin intravenous ZDV in mother, give single dose nevirapine to mother and child, oral ZDV for infant, consider delivery by C-section.

Answer: Begin intravenous ZDV in mother, give single dose nevirapine to mother and child, oral ZDV for infant, consider delivery by C-section.

The New England  
**Journal of Medicine**

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Volume 331      NOVEMBER 3, 1994      Number

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

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FOR THE PERINATAL AIDS CLINICAL TRIALS GROUP PROTOCOL 075 STUDY GROUP\*

### Antepartum Management

- Offer voluntary HIV screening to ALL pregnant women.
  - Repeat screening at late third trimester
- If HIV positive, determine clinical and laboratory stage.
- Begin ZDV as part of ARV after 14 wks
  - Avoid efavirenz
- Monitor ZDV toxicity.
- Intrapartum intravenous ZDV

### Mode of Delivery and Risk of Perinatal HIV infection

- Meta Analysis of 8533 mother-child pairs shows that elective Cesarean section reduces the risk of transmission from mother to child independently of the effects of treatment with ZDV.

NEJM April 1999.

### Recommendations for Cesarean Delivery

- Scheduled C-section at 38 weeks for mothers with VL > 1000 copies
- Consider in mothers with no pre-natal care or antepartum ARV
- Begin iv ZDV 3 hrs prior to scheduled C-section.

### Treatment of Infants born to HIV-infected mothers

- ZDV started w/in 12 hours of birth
  - >35 wks 4po/3iv mg/kg q 12 hr
  - >30- < 35 wk 2mgpo/1.5iv mg/kg q 12 then q 8 @ 2 wk
  - <30 2po/1.5iv mg/kg q 12 then q 8 @ 4 wk
- Infants born to mothers with no antepartum ART.
  - ZDV for 6 wks plus Nevirapine birth, 28, 96 hours

### Management of HIV+ pregnant women who have not received ART prior to labor

- Consider delivery by C-section
- Continuous iv ZDV (2mg/kg loading dose and 1 mg/kg/hr) during labor
- Single oral nevirapine 200 mg, at labor onset
- Single oral nevirapine 2mg/kg for infants
- Oral ZDV 2mg/kg q 12 hours for 6 weeks for infant

### Infant management

- Mother should not breast feed the infant
- Begin PCP prophylaxis at 4-6 weeks for all infants until status is known
- Routine immunizations for HIV exposed infection until status is known (this include Rotavirus).

### Laboratory evaluation of HIV-exposed Infants

- CBC birth, 4, and 8 wks, to monitor ZDV toxicity, reduce dose if needed
- PCR for HIV DNA
  - Birth\*
  - 14 days
  - 2 months
  - 4 months

### CASE 3: OUCH!!

- You are drawing blood from a 6 week old infant born to an HIV+ mother and suffer an inadvertent needle stick to the palm of your hand.
- The child had a negative PCR at birth and has received appropriate ART to prevent MTCT.
- What should you do next??

### Now what do you do?

- Notify your employer of the needle stick and obtain immediate medical exam and blood testing for HIV.
- The child has a <5% chance of being infected, there is minimal risk, do nothing.
- Start yourself on antiretroviral therapy immediately.
- Find out the child's PCR results and if positive start combination ART.

### Your risk

- If infected, the child has acute viremia and high viral load (CDC class 2 risk) thus 3 drug post exposure prophylaxis is recommended started within 12 hours of exposure.
- If HIV PCR is negative, consider stopping ART
- Use barrier method of contraception, avoid Breast feeding, blood donations for the next 6 to 12 weeks.
- HIV ELISA testing at time of exposure, 6, 12, and 24 weeks post exposure.

### References

- <http://aidsinfo.nih.gov!!!>
- Revised recommendations for HIV testing of adults, adolescents, and pregnant women in the health care setting, Sept 2006
- Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States, April 2009.
- Updated U.S. Public Health Service guidelines for the management of occupational exposure and recommendations for post exposure prophylaxis, Sept 2005.