

HIV/AIDS Update

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June 5, 1981 MMWR: Pneumocystis Pneumonia - Los Angeles

“In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *P. carinii* pneumonia at 3 different hospitals in Los Angeles, CA. Two of the patients died. All 5 patients had laboratory confirmed previous or current CMV infection and candida mucosal infection.”

**Now estimated to have entered the human population
between 1902 and 1932!**

Milestones:



1981

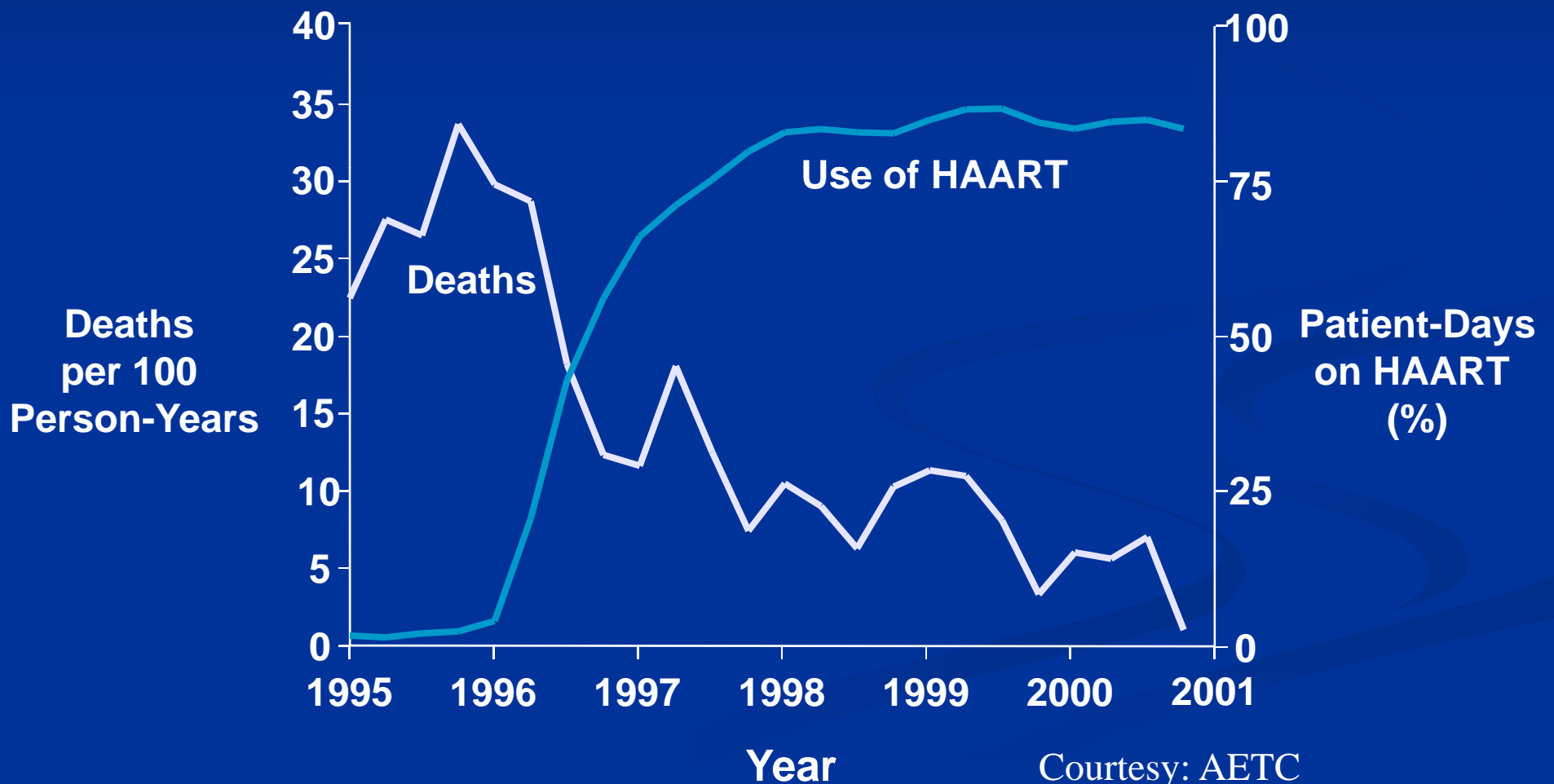
- Over next few years, found to be due to a virus initially called HTLV-III
- Mid 80's: estimated 20 yrs for vaccine to become available
- **1985** - Ab testing available for screening U.S. blood supply

Milestones:

- Late 1980's/early 1990's - single drug rx
 - CD4 counts found to be useful markers for progression of disease
 - Treatment (at CD4 of < 500), when available, very toxic, very inconvenient, and short-lived
 - Later, commercial availability of viral "loads"
- **1996** - recognition that triple drug "cocktails" were reasonably effective at controlling progression of disease while limiting rapid development of resistance
Downside: very high pill burden, many serious side effects
- Currently: (for many) one pill/day!!!!

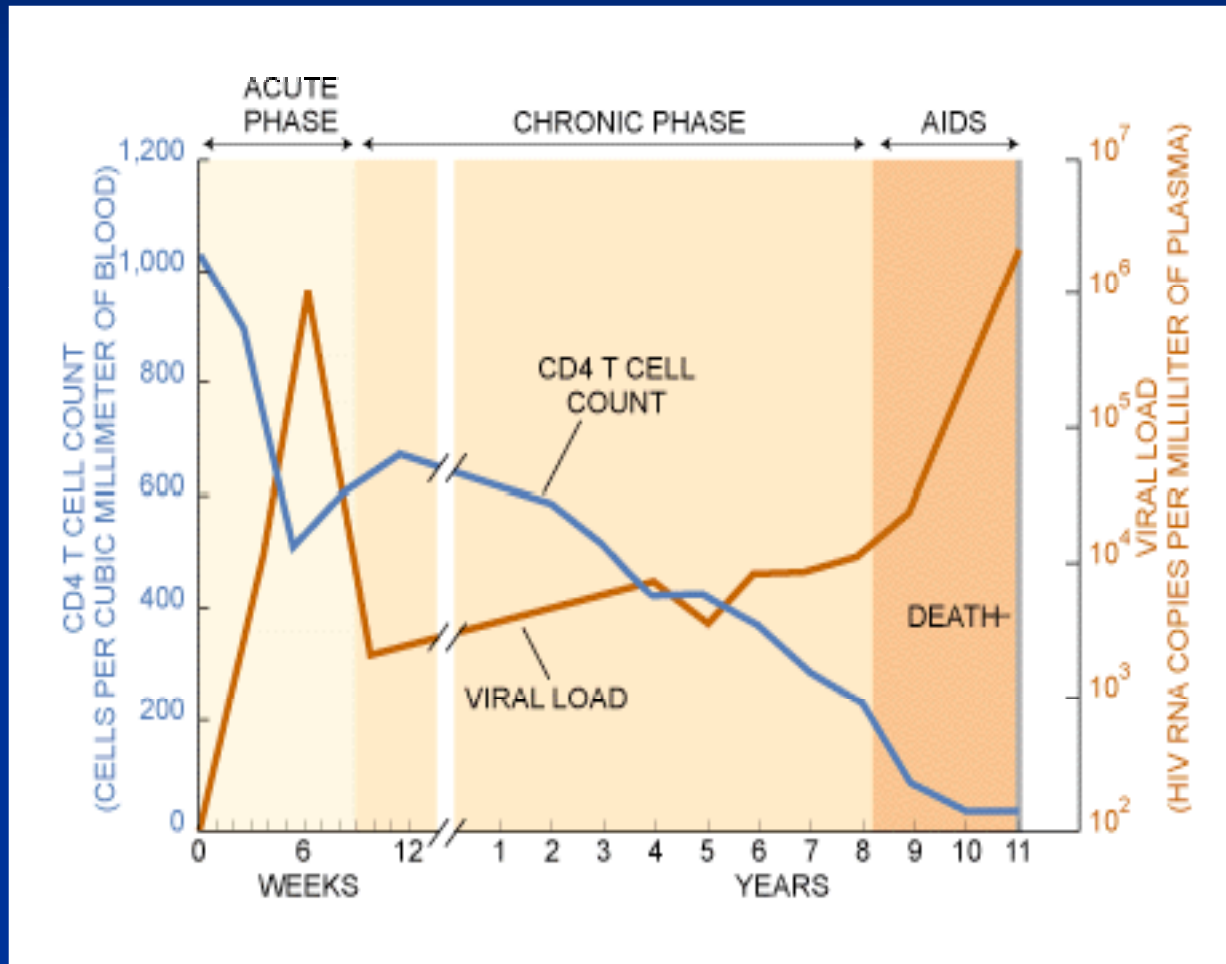
Mortality vs HAART Utilization

HOPS Study



Courtesy: AETC

Natural History of HIV



Courtesy: AETC

Currently in the U. S. alone....

(data thru 2008)

- ~1,180,000 **HIV+**
- ~468,000 living w/ **AIDS**
 - 37,000 newly diagnosed each yr
 - 14,500 die each yr
 - Cumulative U.S. deaths from AIDS thru 2007 : 583,000
- 50 - 56,000 newly infected each yr
 - 1 infection every 9 1/2 minutes
 - >1/2: MSM (1/2 unaware of being infected)

“But I Thought.....”

- 1 of every 5 gay urban males HIV+
- 1 of every 22 African Americans will be infected
- **Est. 21% (230,000) unaware of their HIV+ status**
- **Only 19% of all HIV infected individuals are estimated to have undetectable virus and are therefore (close to) non-contagious.**
This means that over 800,000 have detectable virus and are therefore **CONTAGIOUS!**
- **Individuals unaware of their HIV+, particularly those recently infected, are major contributors to the ongoing epidemic**

Worldwide.... (data thru 2006/7)

- 33,000,000 living with HIV/AIDS
 - ~2/3 sub-saharan Africa, mostly hetererosexual
 - 7000 new infections each day (2.6 million/yr)
 - 1200 of these are children < 15 yo
 - 2,000,000 die each yr
- 15,000,000 orphans
- Only 25% of eligible candidates are receiving tx

The epidemic continues.....

You will most likely see....

- Individuals - some w/ very high risk behavior - that are unaware that they are HIV+, or are in denial about their HIV status or at-risk behavior, e.g. “down low”
You may be completely unaware of their high-risk behavior
- HIV+ individuals cared for elsewhere by an “HIV Specialist”, but are seeing you for other reasons

Or....

- As a result of screening and more liberalized testing, including part of routine care
 - Blood donation
 - Insurance exam
 - “Just in case”
- “Acute Retroviral Syndrome”
- **Still common:** Opportunistic infection “O.I.” or HIV-associated malignancy as initial presentation
- Or, you might be involved in an “exposure”

- A 32 y.o. caucasian female asks her PCP or gynecologist to test her for HIV as he is writing out her 3rd prescription for Diflucan ® within the past year
- Surprise!! Her HIV test is positive

- This 22 y.o. A college student develops high fever, severe sore throat, myalgias, diffuse adenopathy, and a rash, leading to a visit to your office
- PMH: “acute mono” when he was 13 y.o.
- His pharynx is erythematous; a white exudate is noted on his tonsils.
- Strep screen and mono spot: negative
- CBC: 3400
- If you even think to ask, he has the same girl friend for the past 3 yrs

Acute Retroviral Syndrome

- Fever (96%), adenopathy (74%), pharyngitis (70%), rash (70%) myalgia (59%), thrombocytopenia (45%), leukopenia (45%), diarrhea (37%), headache (32%)
- **2/3 have a mononucleosis-like syndrome**
- May also present as “Aseptic/viral meningitis”
- Incubation period: 1-6 weeks; resolves within 15 days (w/o treatment)
- Though HIV Ab may be negative, this individual is likely to be highly contagious

So where did he get this??

“Down Low”

- In long term heterosexual relationship, but w/ discreet episodes of MSM

Still Common: PCP (PJP) (*P. jirovecii*) “YEE ROW VET ZEE”

- Subacute to acute pneumonia - still a common presentation in patients who are unaware of their HIV status or are otherwise untreated
- **Steroids** if $pO_2 < 70$



See JAMA: June 24, 2009

Other clues to possible HIV:

- Unusual presentation of a common illness
 - Pneumococcal pneumonia w/ bacteremia in a young person
 - Salmonella, shigella, campylobacter bacteremia
- Presentation of an unusual illness
 - Uncommon dx
 - More advanced/severe dx than expected
 - Unusual age for illness
- TB, especially w/ unusual presentation
- Other STDs



Correlation of CD4 count to presentation of Opportunistic Infections

- Infections common in the non-HIV infected population tend to occur at higher CD4 counts.
At lower CD4 counts these same infections may also occur, but often with more extensive, disseminated or recurrent disease. (TB, HSV-1/2, H. zoster, various neoplasms, candidiasis)
- Infections rarely, if ever, seen in the non-immunosuppressed host tend to occur at the lowest CD4 counts, e.g. disseminated CMV, MAC
- Malignancies more common, even w/ “adequate” CD4 ct

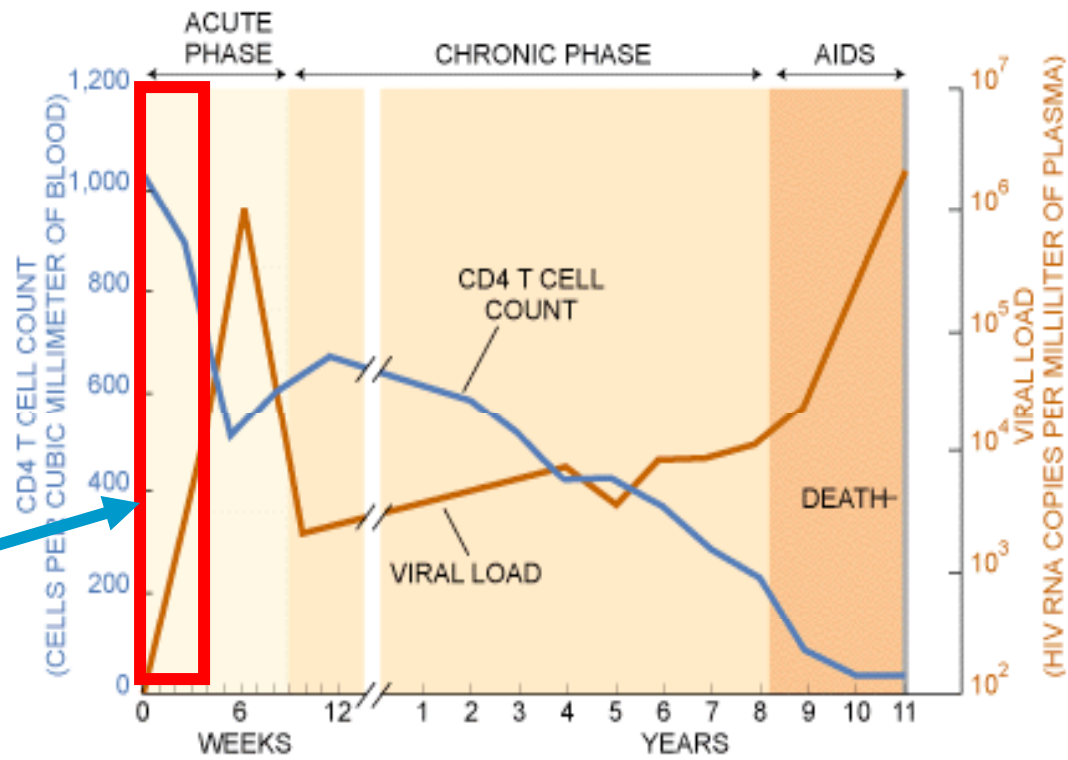
O I's/neoplasms relative to CD4 counts

- 200 - 500 and above
 - Pulmonary TB
 - **Bacterial pneumonia**
 - Oral/vaginal candidiasis
 - H. zoster
 - Cervical CA, Kaposi's sarcoma, Hodgkin's lymphoma
- 50 - 200
 - **PCP**
 - Disseminated TB
 - Esophageal candidiasis
 - Cryptococcal meningitis
 - CNS toxoplasmosis
 - Cryptosporidium
 - Non-Hodgkin's lymphoma
 - Disseminated histoplasmosis, coccidioidmycosis
- Lower
 - CMV, MAC

Diagnosis

- **Screening: ELISA antibody (or other rapid tests)**
 - **New: testing now recommended to be part of routine medical care (yearly if high risk)**
 - Likelihood of true positivity depends on patient population being screened
 - Time to positivity: ~ 3 wks, most all + within 6 - 8 weeks
- **Confirmation: Western Blot**
 - **Time to positivity: ~4-5 weeks**
 - Any two: p24, gp41, gp120/160 -> positive
 - one + band, or other + bands -> “indeterminate”
 - if low risk situation - usually false +
 - if high risk situation - may be early true +

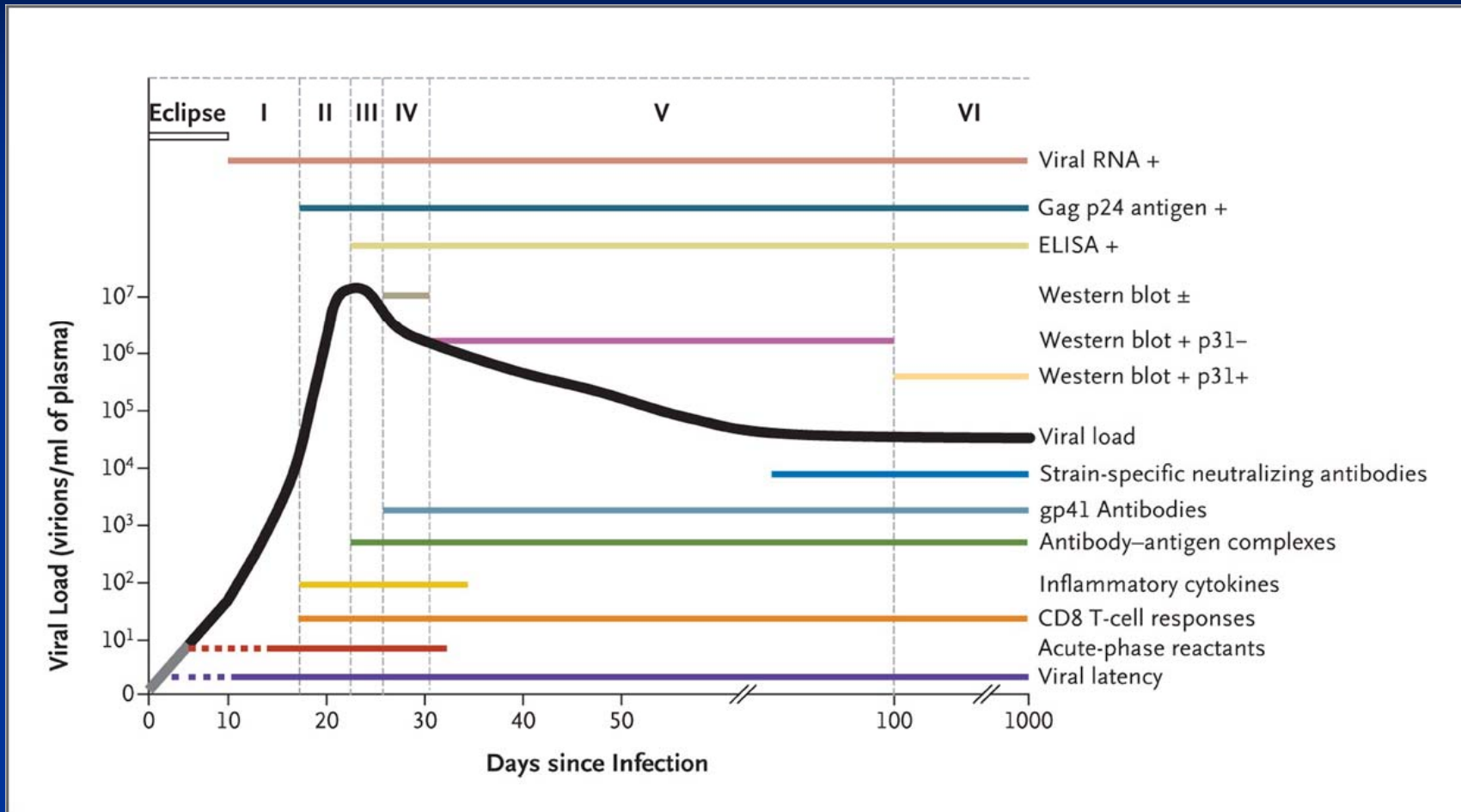
But.....



Window phase-
Tests neg for HIV

Courtesy: AETC

Natural History and Immunopathogenesis of HIV-1 Infection.



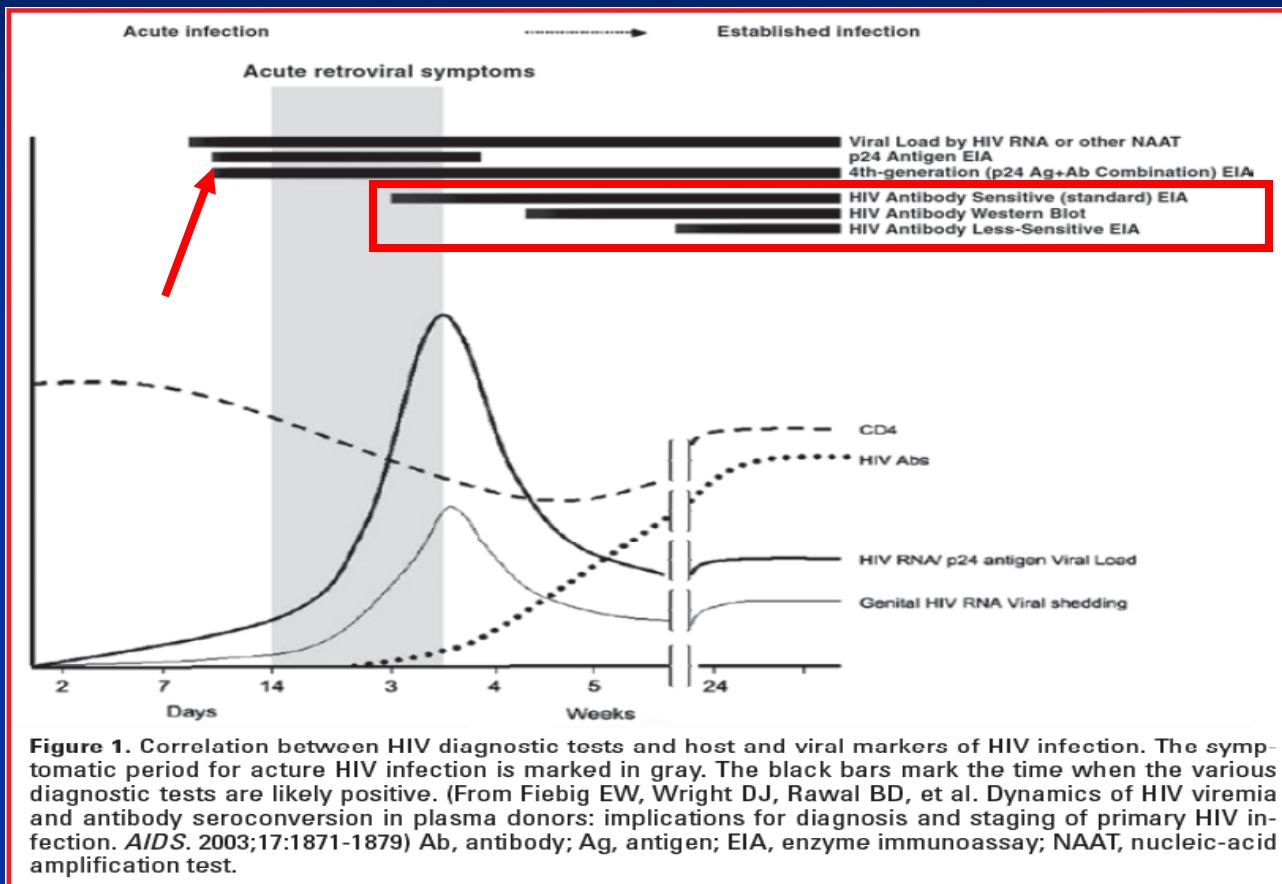
Cohen MS et al. N Engl J Med 2011;364:1943-1954.



The NEW ENGLAND
JOURNAL of MEDICINE

“Window phase”

- For at least the first 3-4 weeks following infection, traditional screening tests negative; however, **during this time frame, highly contagious**
- Quantitative assay for HIV by PCR
- **Newer qualitative assays, including NAT, p24 ag, etc., shortening time to positivity by ~ 1 week**
- **Abbott's 4th generation assay - “Architect”®**
 - + by 2nd week?
 - 30 minute turn-around-time



Source: Marquez, MLO February 2008. "HIV Testing: An Update"

Courtesy: Abbott Laboratories

Why emphasize early diagnosis?

- **Individuals unaware of their HIV+, particularly those recently infected, are major contributors to the ongoing epidemic**
- **Current trends are towards earlier treatment, both for the presumed benefit of the individual as well as society**

Clinical Course

- Without treatment, median time to develop “AIDS” is around 10 years
- Both viral properties and host/genetic factors affect progression of disease
- Viral load:
 - Correlates with degree of contagiousness, rate of immune deterioration
 - **NEW:** “Cumulative viremia” w/ its subsequent persistent inflammatory response to this may be responsible for many of the long term complications of HIV
- CD4 lymphocyte count:
 - Reflects immune status (as affected by VL)
 - Correlates w/ development of opportunistic infections (OI's) and, to some extent, malignancies
 - Restoration may approach normalcy, but probably never completely; earlier tx may be more beneficial in this regard

Treatment

- “old”, but still valid: HIV destroys the immune system.
- Treatment:
 - Improves immune system by (partially) restoring CD4 count
 - Lowers mortality
 - Earlier tx may lower long-term complications
 - Earlier tx may lower rates of extensive triple class tx failure (resistance)

- **New: HIV is a chronic viral infection w/ chronic inflammation and persistent stimulation of the immune system, leading to:**
 - Increased risk of CV and other dx usually associated w/ aging
 - Increased risk of malignancies, particularly if very low CD4 count prior to tx
 - 27% of HIV-related deaths due to HIV-related malignancies
 - Risk of NHL > 76 times that of non-HIV infected individual
- Earlier treatment may mitigate some of these adverse effects, though biomarkers of inflammation may never return to normal

When? (only when pt ready):

- symptomatic, or “AIDS-defining” illness
- Old: CD4 count < 200
- More recent: CD4 count < 350
- **Newer: <500 or....
at diagnosis (“Test and Treat”), regardless of CD4 ct**
- Pregnancy
- HIV-associated nephropathy (to preserve kidney function)
- Active hepatitis B or C coinfection
- HIV RNA > 100,000 copies/ml
- High risk for secondary transmission

HIV and Pregnancy

- Overall risk of transmission if infected mother not identified (and not on tx): 25-33%
- IF infected mother identified (and appropriately treated): 1-3%
- Test at initial visit **and at near term**

Treatment

- Goal:
 - viral load “undetectable”, followed by an increase in CD4 count
- Duration: indefinitely
- Treatment cannot be given intermittently (“STI”)

Immune Reconstitution Inflammatory Syndrome (“IRIS”)

- An exaggerated inflammatory response to a previously relatively quiescent condition as a result of restoration of immune competence following initiation of HAART
 - e.g. focal MAC dx,
 - CMV vitreitis
 - TB
 - Cryptococcal meningitis
 - Hepatitis C
 - PML
 - HSV
- Risk factors:
 - Antiretroviral naïve
 - Starting HAART w/in 30 days of a diagnosis of an OI
 - Rapid decrease in HIV RNA level in response to Tx
- Tx: continue HAART, therapy of specific condition, Rx anti-inflammatory agents

Primary Prophylaxis against OI's*

PCP	CD4 < 200	TMP-SMX
TB	Previous + PPD** or +PPD > 5mm	INH x 9 mos
Toxoplasmosis	+ serology w/ CD4 < 100	TMP-SMX
M. avium complex	CD4 < 50	azithromycin or clarithromycin

*can usually be d/c'd upon return of CD4 count to above threshold parameters after ~3 months

**QFG assays probably similar to PPDs, but also w/ the same difficulties in interpretation in some situations

- While performing an office procedure, you manage to penetrate one of your gloves - and your finger - w/ the bloody scalpel blade.

This patient's HIV status is unknown/presumably negative.

- Now what??

- Hepatitis Bs Ag
- Hepatitis C Ab
- HIV Ab - time is critical - the most rapid test you have available

- **If pt found to be HIV + (or if this information will not be forthcoming), immediately call PEP hotline: 1 - 888 - 448 - 4911**

- While performing an office procedure, you manage to penetrate one of your gloves - and your finger - w/ the bloody scalpel blade.
- Your worst nightmare: this patient has advanced HIV and is a terrible historian.
It's Friday night - all the I.D. docs are at the bar.
- Now what??

If you know the patient is + :

- What HAART (if any) is he/she on?
- What previous regimens has he/she been on?
- What is their “viral load”
- **PEP hotline: 1- 888 - 448 - 4911**
- **There has been no documented occupational injury leading to transmission of HIV since 2001!**

“I have this friend.....”

- After partying way too much this weekend in San Antonio, your pt calls you in a panic Monday am.

He thinks he had unprotected sex the night previously, but can't remember the details. He sheepishly admits that his wallet was empty the following morning.

- Call the PEP Hotline (“nPEP”)

Earlier Rationale for Tx:

- For waiting until CD4 < 200:
 - Limited resources
 - High pill burden and drug toxicity
 - This CD4 ct predicted poor prognosis
- For CD4 of 200 - 350:
 - Better response/prognosis
 - If wait until <200, many never regain a normal or near normal CD4 count

Earlier Rationale for Tx:

- For treatment at higher CD4 counts (between 350 to 500) (This in the face of improved tx options)
 - Considering likely life-long tx, earlier rx does not add that much to overall picture
 - Much less toxicity
 - Much less pill burden
 - Even better prognosis
 - **Decrease complications associated w/ long term inflammation**
 - Cardiovascular dx
 - Malignancies

The Latest Rationale:

- For treatment at even higher CD4 counts (>500), including “Test and Treat” strategies
 - “Delayed Therapy” group (<500) had 94% higher mortality!*
 - More complete restoration of immune system?
 - Decrease complications associated w/ long term inflammation?
 - Decrease spread of HIV - (controversial) societal vs individual benefit
- Also controversial:
 - Rx long term sexual partners?
 - Rx commercial sex workers?

*Kitahata et al.

Additional issues:

- Circumcision:
 - Decreased acquisition by heterosexual men in Africa by 50-60%
 - Decreased transmission by HIV+ males to their heterosexual partners by 30%
 - Decreased some (not all) other STDs as well
- Vaginal gel (Tenofovir):
 - Decreased acquisition by 1/2 at 1 yr (though only used 60% of time)
 - Newer future formulations and better compliance likely to be even more effective
 - Decreased acquisition of genital herpes by 1/2 as well

Additional issues:

- PrEP (Preexposure Prophylaxis)
 - Controversial
 - Once daily Truvada ®
 - Widely varying protection averaging ~ 44%
- nPEP (Non-occupational Postexposure Prophylaxis)
 - ~72 hr window for intervention
- Vaccine:
 - Largely heterosexual population
 - Initially ~30% effective, but benefit may have decreased over the first year after vaccination

FAQs re: Risk

- **Transmission is highly correlated w/ Viral Load**
- If transfused w/ contaminated blood: 95%
- **Perinatal transmission if mother not under tx: 25%**
- Needle sharing: 1 in 150
- **Occupational needle stick: 1 in 300 (0.3%)**
- M-M receptive intercourse: 1 in 10 to 1 in 1600*
- M-F vaginal intercourse 1 in 200 to 1 in 2000*
- F-M vaginal intercourse: 1 in 700 to 1 in 3000*
- **Other scenarios: ?, but NOT ZERO**

*assuming not on Tx or w/ undetectable VL

“Take Homes” - Summary I

- HIV remains an epidemic with high mortality, in part because...

Relying on your ability to judge who is at risk for HIV is, at best, unreliable, and...

- 20 - 25% of HIV infected individuals do not know they are infected, and...
 - Acutely infected individuals are extremely contagious
 - For multiple reasons, est. only 19% of all HIV infected individuals in this country are adequately treated, and therefore minimally to non-contagious
- **Effective treatment can reduce risk of transmission to near zero!!**

Summary II

- Major trend is now towards much earlier identification and treatment of HIV+ individuals - e.g. “Test and Treat”
- Current treatment (often only 1 tablet/day) is both safe and effective if the pt is adherent, making possible a normal, or near normal lifespan
- Though controversial, both nPEP (at least somewhat) and PrEP are effective

Summary III

- With effective treatment:
 - Better long term survival
 - Even with return of CD4 towards or to “normal”, immune restoration may be incomplete
 - Potential long term benefits of decreased inflammatory state
 - Treated patients are much less contagious
- But.....
 - Complacency about high-risk behavior among certain populations remains very problematic
 - Access to diagnosis and treatment extremely limited in many parts of the world
 - 11 states currently have waiting lists for treatment!

Thank You

Don't forget the PEP #

1 - 888 - 448 - 4911

References

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