HIV – What (more) do we need to know?

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It's 2013 –
Is your manual up to date?

- How long have you been underwriting?
- Much of what you learned about HIV in the past may now be WRONG.
- Or, you may have been taught very little about HIV in your underwriter training.
- Why now is there a WAHLU presentation on HIV?

Fasten Your Safety Belts!!!

Retro-Underwriting - 1990

- 27 y/o male applies for $100,000 of permanent life
- Diagnosed with AIDS 2 years ago after presenting with *Pneumocystis* pneumonia
- On multiple preventative meds, but only one HIV med
- Estimated life expectancy: +/- 2 years
- Underwriting assessment: uninsurable risk

Modern-Underwriting - 2013

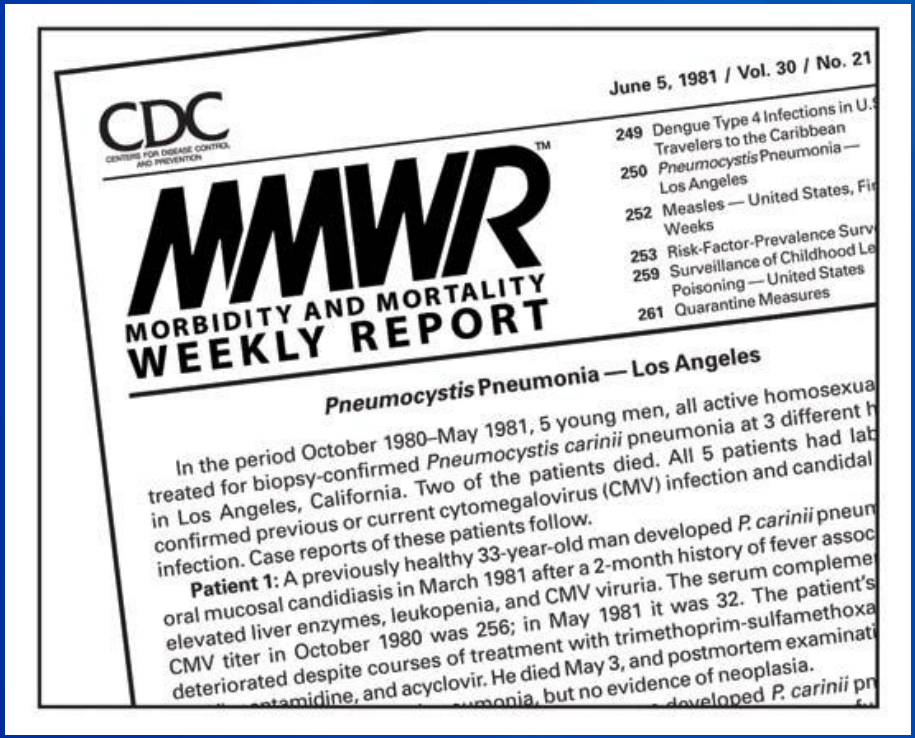
- 27 y/o male applies for $1,000,000 of permanent life
- Diagnosed with HIV 2 years ago by primary MD during recommended CDC screening
- Takes Atripla, once daily, otherwise healthy
- CD4 count is 745, viral load is undetectable
- Estimated life expectancy: ?
- Underwriting assessment: ?

Getting Up to Speed on HIV – Today's Talking Points

- A History Lesson
  - Reintroduction to an old foe
- A Science Lesson
  - Knowing and speaking the *language* of HIV
- HIV Today: What do we *already* know?
  - Mortality studies
  - Risk stratifiers
- What (more) do we need to know?
  - Insurability depends on…
- Vaccine and Cure
- Wrap-up and take-home messages

A History Lesson

- Mid-20th century (or earlier) – non-human primate virus (SIV) "jumps" to humans
- 1981 - MMWR report
- 1982 - Dr. Z starts college



June 5, 1981 / Vol. 30 / No. 21

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

MMWR™
MORBIDITY AND MORTALITY WEEKLY REPORT

249 Dengue Type 4 Infections in U.S. Travelers to the Caribbean
250 *Pneumocystis* Pneumonia — Los Angeles
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261 Quarantine Measures

***Pneumocystis* Pneumonia — Los Angeles**

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

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneun oral mucosal candidiasis in March 1981 after a 2-month history of fever assoc elevated liver enzymes, leukopenia, and CMV viruria. The serum compleme CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's deteriorated despite courses of treatment with trimethoprim-sulfamethoxa ntamidine, and acyclovir. He died May 3, and postmortem examinati umonia, but no evidence of neoplasia. developed *P. carinii* pn

History…

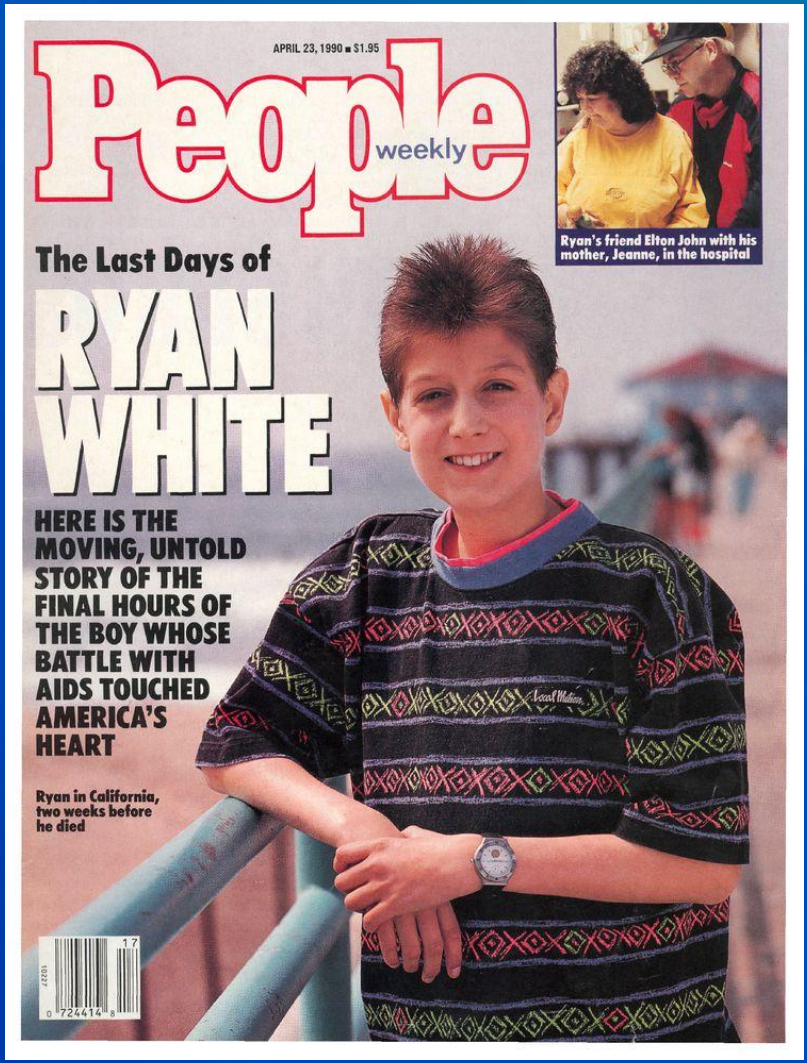
- 1983 – HIV isolated (Gallo or Pasteur?)
- 1985 – blood test for HIV antibodies became available
- 1986 – Dr. Z starts med school
- 1987 – AZT approved
- 1987 - Reagan mentions HIV for first time

History…

- 1988 – Greg Louganis wins gold at Seoul Olympics

History…

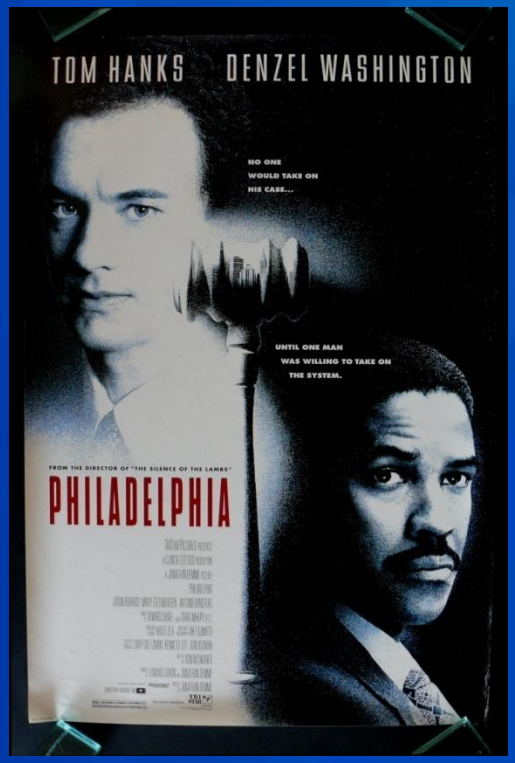
- 1990 - Dr. Z starts residency
- 1990 - Ryan White dies
- 1991 – Magic Johnson announces he is HIV+



History…

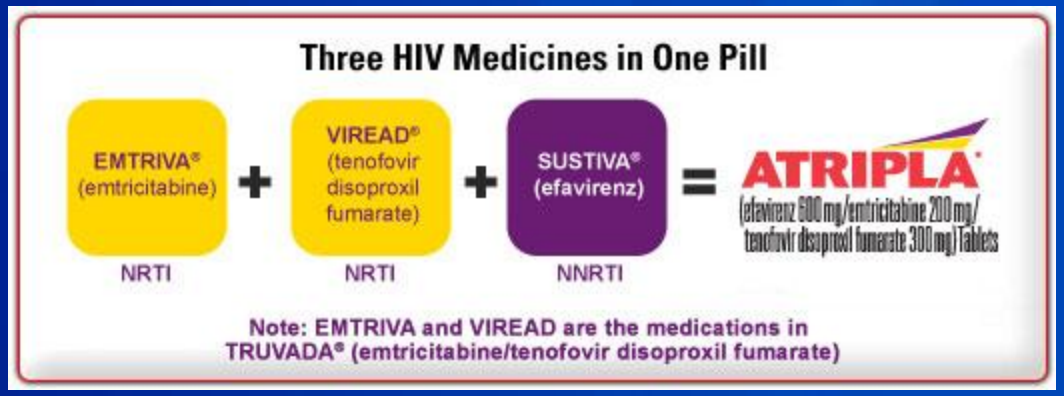
- 1992 – Multi-drug therapy becomes available

- 1993 – the movie *Philadelphia* is released



History…

- 1995 – 1st protease inhibitor (saquinavir) approved – HAART (highly active anti-retroviral therapy) begins
- Early 2000s – HIV referred to as a "chronic disease"
- 2006 – Atripla approved – "one pill, once daily"



www.atripla.com

History…

- 2006 – CDC recommends testing everyone age 13-64
- 2008 – annual incidence of new HIV infections in U.S. raised to 56,000
- 2012 – OTC 20-minute HIV test

www.oraquick.com

How did the life insurance industry respond to HIV/AIDS?

Main Concerns and Actions Taken	
Business "on the books"	**New Business**
Creation of AIDS reserves	Testing – antibody vs. other surrogate tests
Adjustment of premiums	Stopped writing policies in certain jurisdictions

- American Council of Life Insurers - ACLI
  - Member companies played major role in ACLI response to legislative and regulatory challenges

Society of Actuaries - SOA

- 1987 – SOA: "AIDS, HIV Mortality and Life Insurance"
  - AIDS diagnosis to death = 2.1 years
  - 1986: $200 million in individual and group claims (1%)
  - By mid-1990s AIDS could account for 10% of life insurance claims
  - Expected total claims by year 2000 - $30 billion!

Source: Cowell, M., Hoskins, W. AIDS, HIV Mortality and Life Insurance, SOA, August 1987

HIV and Life Insurance

- 1997 - an IL company offers coverage to HIV patients, but closes down this line in 2004
- The Europeans and South Africans have begun to offer coverage, but they have *different*…
  - business conditions
  - social drivers
  - products than offered in North America (NA)
- October 2012 – a NA reinsurer announces it will review individual HIV cases for up to $1 million in coverage

A Science Lesson: HIV 101

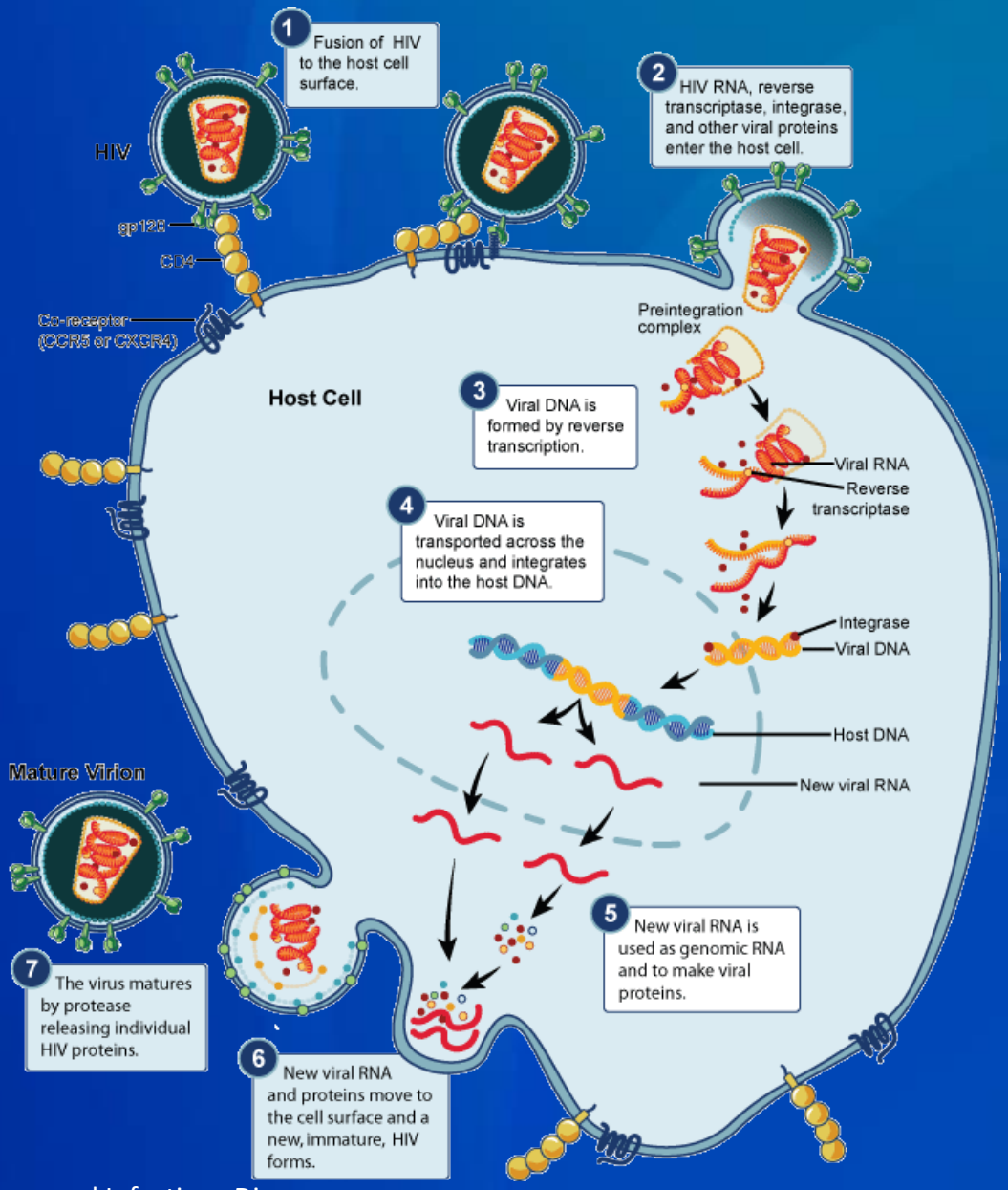
- Terms you need to know and the "Life Cycle" of HIV
- Epidemiology
- Testing
- HIV's effect on the immune system
- HIV-infection vs. AIDS
- Treatment and its impact

Terms you need to know

Term	Description/Definition
HIV	Human Immunodeficiency Virus
AIDS	Acquired immune deficiency syndrome
CDC	Centers for Disease Control and Prevention
CD4 cells = T helper cells	Subset of WBCs which are targeted by HIV Normal range: 500 – 1300 cells per microliter
Viral load	Number of HIV virus particles measured in the plasma by PCR Reported as # per ml or as log (multiples of 10)
HAART = ART= cART	Highly active anti-retroviral therapy = anti-retroviral therapy= combination anti-retroviral therapy

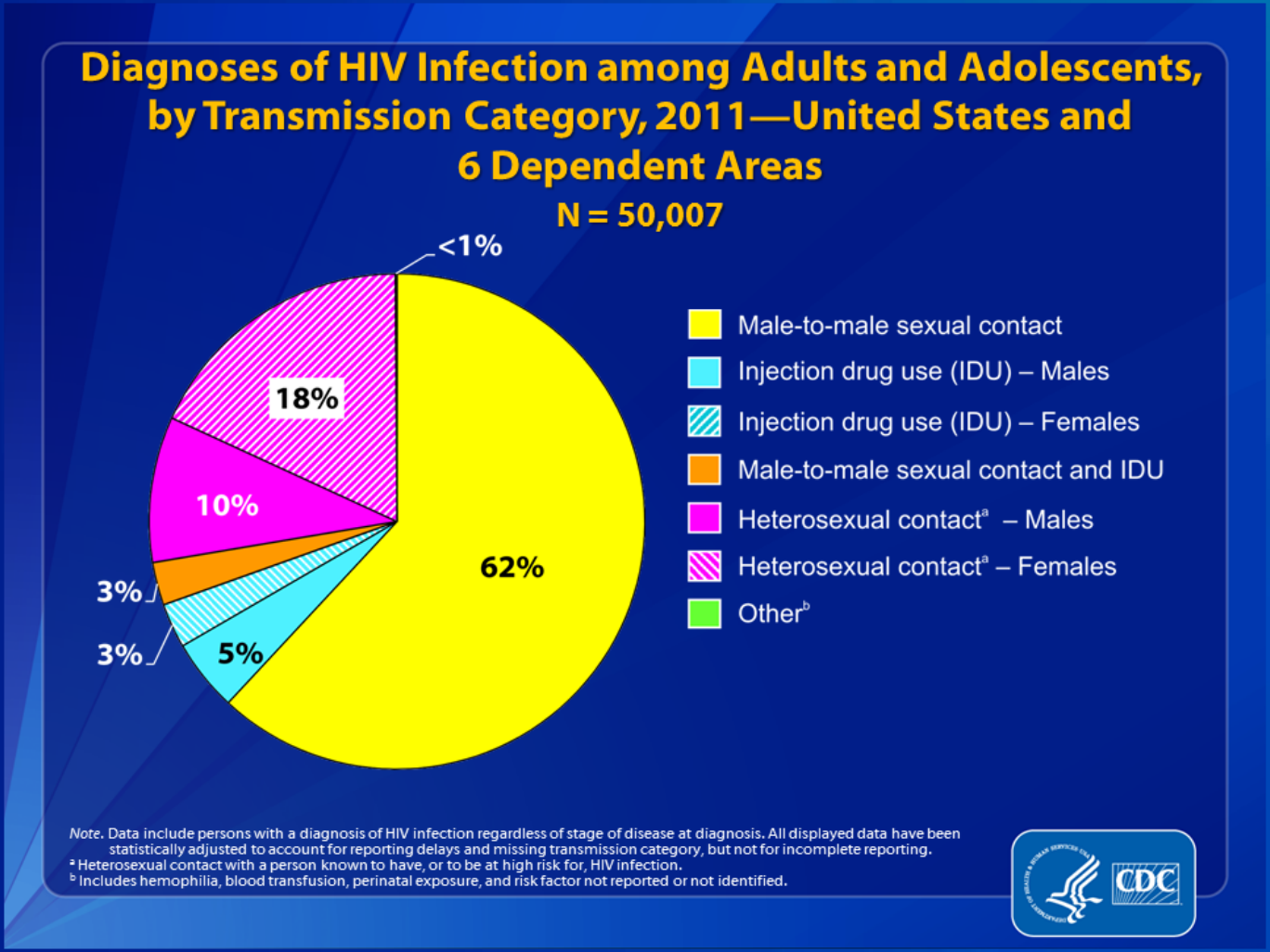
HIV Lifecycle

1. Fusion with host
2. Viral contents enter host
3. Reverse transcription
4. Integration
5. Transcription
6. Assembly
7. Budding of new viruses



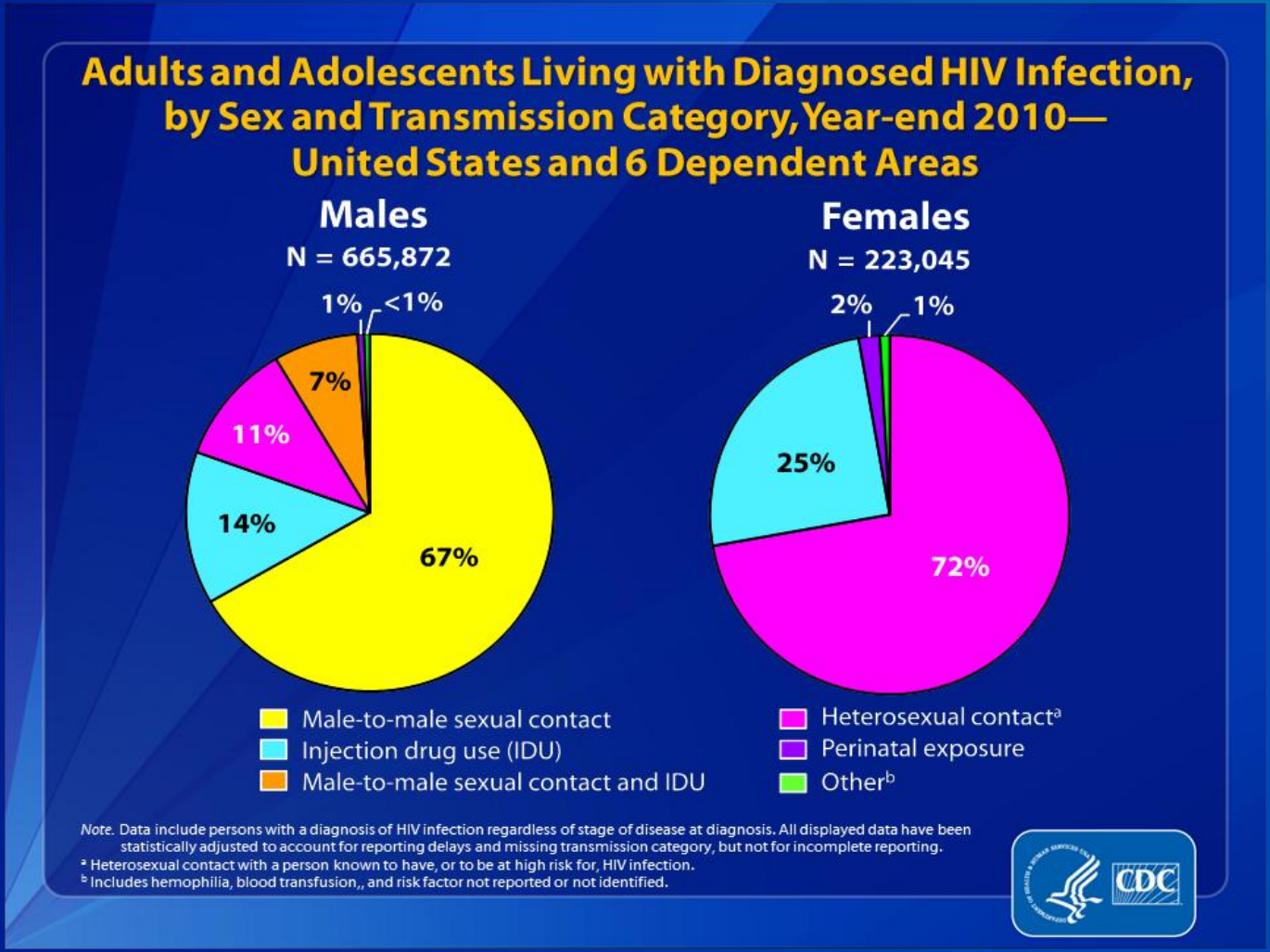
Source: National Institute of Allergy and Infectious Diseases

HIV: Who gets it?



Source: Centers for Disease Control and Prevention

HIV: Who's got it?



HIV: Who's got it (by age)?

Age Range	Number
13-24	68,900
25-34	164,000
35-44	304,000
45-54	380,900
55-64	155,700
>64	40,300
Total	1,113,800

2006->2009 Source: CDC (June 2012 Report)

Who's got it (by age)?

- 17% of new HIV infections occur in those over age 50.
- By 2015, half of those living with HIV will be over 50 years of age!
- Explanation -> living longer....

HIV Testing

- ELISA (enzyme-linked immunosorbent assay) – screening test
- Western blot - confirmatory
- Immunofluorescence assay (IFA) - confirmatory
- PCR (polymerase chain reaction) = “viral load”
- Insurance lab testing:
  - Current positive rate 0.046%
- Sensitivity and specificity: >99% - the “perfect” test -> no false positives

Source: Personal Communication, Dr. Robert Stout, CRL

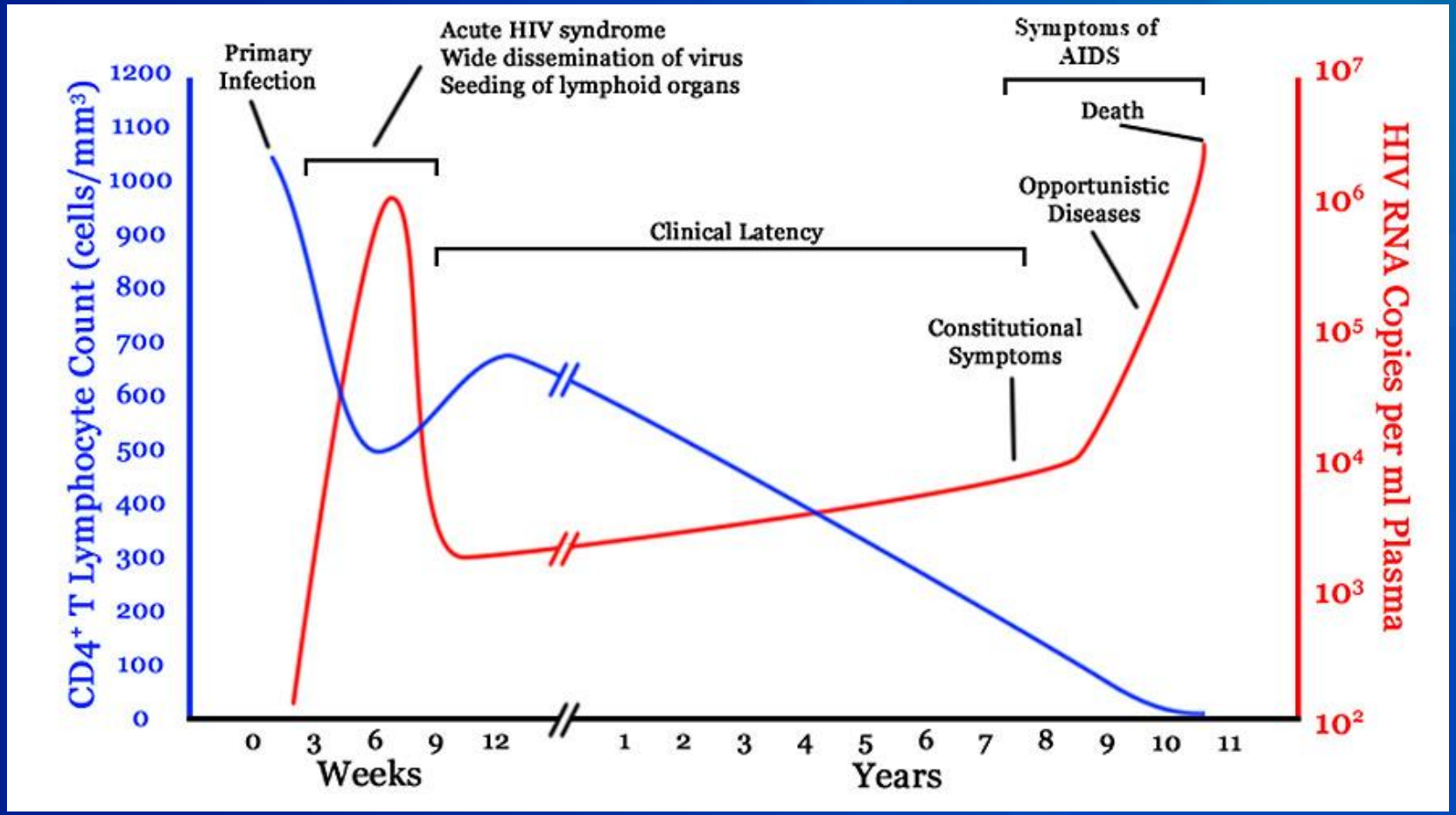
HIV vs. AIDS

"Everyone with AIDS has HIV,
but not everyone with HIV has AIDS."

HIV Stages		
Stage	CD4 count	CD4 %
1	≥ 500	≥ 29%
2	200 – 500	14 – 28%
3 = AIDS	< 200	< 14%
Unknown	No info	No info
Stages 1, 2, and unknown can also be designated AIDS if there are specific clinical conditions present (AIDS defining condition). Note: Viral load not part of staging.		

Source: CDC

HIV's Effect on the Immune System



Note: Course of HIV without treatment

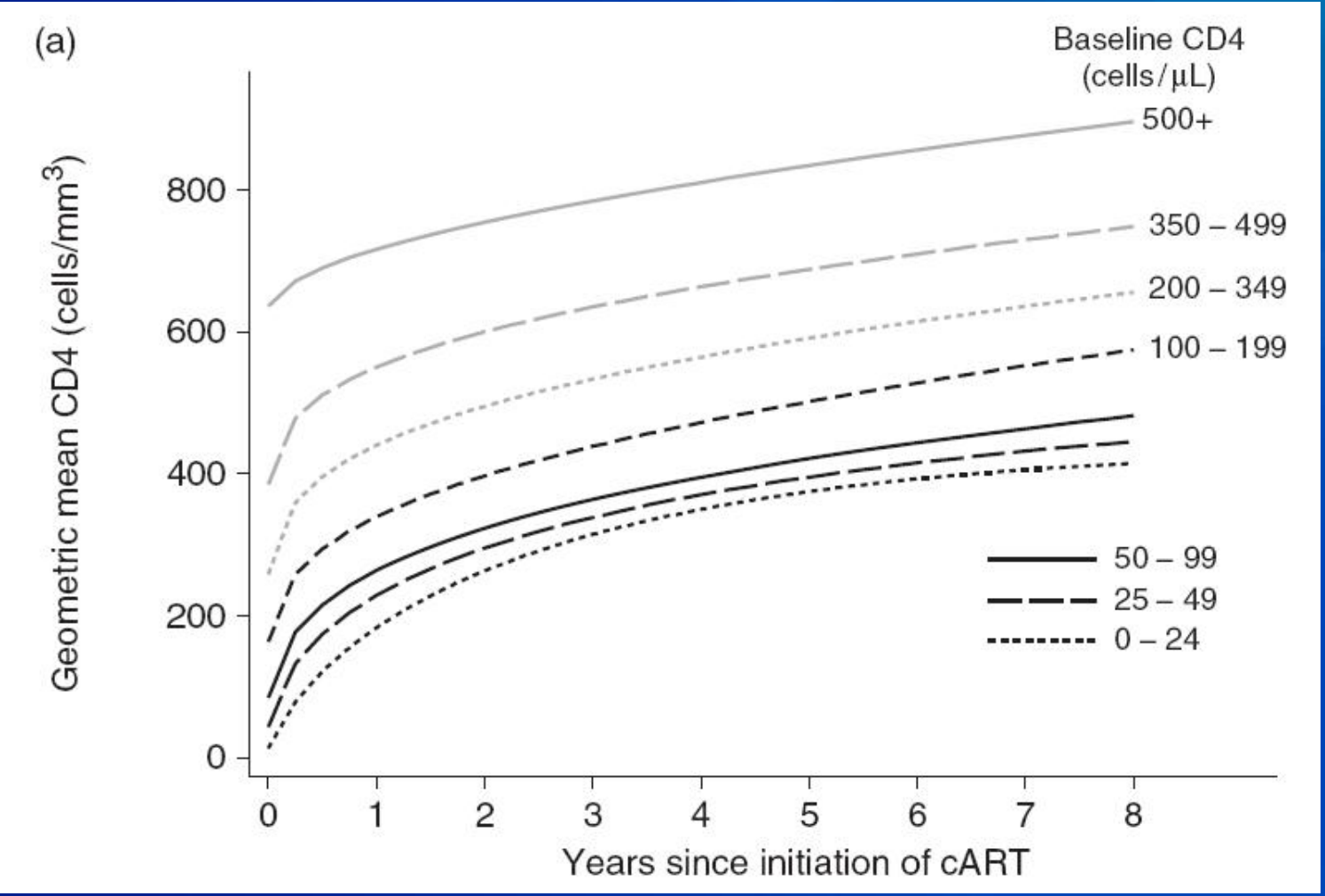
Treatment 2013

- **Multiple classes and combinations of drugs used to treat HIV**

Class Name	First Available
Nucleoside reverse transcriptase inhibitors (NRTIs)	1987
Protease Inhibitors (PIs)	1995
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	1996
Fusion inhibitor	2003
Entry inhibitor	2007
HIV integrase inhibitor	2007

Source: www.fda.gov

Impact of Treatment on CD4



UK Collaborative HIV Cohort (CHIC) study. Hughes RA, et al. HIV Medicine (2011), 12, 583-593

Treatment and Risk of Resistance

- All organisms have the potential to develop resistance
  - Concern with HIV since lifelong treatment required
- What happens if all treatment exhausted?
  - Modeling of impact of resistance over time
  - Median time to “exhaustion” of current meds: 43.4 yrs
- Mitigation of the risk
  - Pre-treatment HIV genotyping
  - Compliance, compliance, compliance

Jansson J et al. Journal of International AIDS Society 2012, 15 (Supple 4): 18077

Treatment and Risk of Toxicity

- HIV treatment is “lifelong”

Side Effects	
Short-Term	Long-Term
Anemia	Lipodystrophy
Diarrhea, nausea, vomiting	Insulin resistance
Dizziness, neuropathy	Dyslipidemia
Fatigue, headache	Low bone density
Rash	Lactic acidosis

- Newer meds safer and better tolerated, but <u>not</u> perfect
- Recent study found no increased risk for increased mortality solely due to long-term med exposure

AIDS 2012 Jan 28;26(3): 315-23

So, what else do we already know?

- Mortality studies since the development of HAART
- Risk stratifiers which impact survival and mortality

There's no shortage of mortality studies!

HIV Mortality Studies

Year	Cohort	Results	Comments
2003	•Swiss HIV Cohort Study (1) •3963 pts followed for median of 3.7 yrs •Excess death rate (EDR), extra deaths/1000/yr calculated	•Overall, EDR 23.9 •Successfully treated, hep c (-) had EDRs of 3.1-3.4	Authors compared short-term mortality of successfully treated pts with cancer patients who have been successfully treated
2004	•Swiss HIV Cohort Study (2) •10977 pts followed for median of 46 mos •Standardized mortality ratios (SMRs) calculated	•Overall, SMR decreased from 79.3 in the pre-HAART era to 15.3 in the HAART era •Best case HAART era SMRs for men and women were 5.2 and 9.5 respectfully	•HAART era mortality remains higher in HIV (+) pts than in Swiss gen pop •Mortality analysis performed irrespective of co-morbid disease, may have over-estimated mortality
2007	•University Hosp, Oslo, Norway (3) •1180 pts •Risk ratio (RR) for 5-yr mortality compared to gen pop calculated pre- and post-HAART	•HAART reduced mortality by 80% •Mortality in HAART era still 4 times > than gen pop	•Study indicates that increased mortality is driven by HIV itself •Exact contribution from HIV requires further study
2007	•Danish HIV Cohort Study (4) •3990 HIV-infected/379872 non-HIV	•Survival at age 25 was calculated to be 38.9 yrs=63.9 •Mortality ratio in most recent time frame calculated to be 570%	•Observed mortality rates are assumed to apply beyond the current max observation time of 10 yrs •Included all persons regardless of CD4 count, HIV RNA, disease stage, AIDS dx, treatment adherence

There's no shortage of mortality studies!

HIV Mortality Studies

Year	Cohort	Results	Comments
2008	•ART Cohort Collaboration (5) •43355 pts followed during three post-HAART time periods •Calculated crude mortality rates and life expectancies	•Mortality rates decreased over the study period •Life expectancy at age 20 years increased from 36.1 to 49.4 = 69.4	•Considerable variability b/n subgroups •Average number of yrs remaining to be lived at age 20 yrs was 2/3 that of non-HIV gen pop •Higher CD4 at initiation had better outcome
2008	•CASCADE (6) •16534 person with median follow up of 6.3 yrs with known seroconversion times •Calculated mortality rates c/w non-HIV gen pop	•Overall reduction in excess mortality of 88% on treatment •Excess mortality rate decreased from 40.8 to 6.1 with treatment	•HIV-infected persons experience mortality rates similar to those in the gen pop in the first 5 yrs following infection, though excess mortality remains as duration of HIV infection lengthens
2010	•ATHENA cohort (7) •4612 HIV +, treatment naïve at 24 wks post diagnosis	•Mortality higher in those with lower CD4 counts •At age 25, years expected were 52.7 (77.7)for men and 57.8 (82.8) for women	•Predictions depend on continuing success of cART beyond the max of 10 yrs of the study duration.
2012	•Cohort: computer simulation model (8)	•Estimated life expectancy of MSM , age 30 = 75 yrs •If low starting CD4 (<140) then 71.5 yrs	•Mathematical model, not actual patients
2012	•UK Collaborative HIV Cohort Study (9)	•Multiple conclusions, but individuals who increase their CD4 in the 1st yr by > 350 have normal LE (80 yrs)	•CD4 at beginning of cART and after 5 yrs of treatment predictive of survival. •Suppression of virus with treatment necessary

Hot Off the Press

- *"Insurability of HIV positive people treated with antiretroviral therapy in Europe: Collaborative analysis of HIV cohort studies"*

- AIDS 2013, 27: 000-000

Study details

- 34,680 HIV patients from 6 European countries
- Started HAART between 1996-2008
- 1,236 deaths through end of 2009
- Looked at actual to expected mortality rates compared to standard insured lives
- Specifically addressed insurability
- Results…

Results

- CD4 count and viral load 6 months after starting treatment highly predictive of mortality
- Gender not significant
- Current age more important than age at initiation of treatment
- Treatment prior to 2001 worse than after
- Mortality ratios decreased with longer treatment
- Outcome stratified by three age groups

Results

- 45 year old with CD4 > 350, viral load < 10000, 6 months after treatment initiated
  - Mortality ratio = 459%

- Conclusion: life insurance can be extended to 20 years coverage for lowest risk HIV

- Assumptions/cautions
  - Extrapolated data beyond 10 years
  - Data is limited above age 60
  - May not be applicable to North America
  - Conclusions limited to 20-year term coverage

What do all the mortality studies tell us?

- Mortality is down, life expectancy is up (a lot)
- Individuals with HIV are a very heterogeneous population
  - Multiple risk stratifiers can be identified
- Study conclusions should be looked at critically
  - Make sure you are comparing apples-to-apples
- Survival estimates, even under the best case scenario (think underwriting), are usually still south of gen pop

Risk Stratifiers

Factor	Best	Average	Poor
Compliance w/ Rx	100%	< 100%	
CD4 count	>500	200 – 500	< 200
Viral load	Undetectable	Any	
HIV Stage	1,2	3 = AIDS	
When Rx started	Soon after infection or Late HAART era (after ~2003)	Later in the course of HIV Earlier HAART era (before ~2003)	
Tobacco/EtOH	None	Any use	
Hep B/C	Hep B/C (-)	Depends if treated/resolved	
IDU	None	Any	
Gender	Inconsistent, but possibly slightly better for women		
Age at diagnosis	Variable, may be better older (relatively)		

So...
what more do we need to know?

- Are we satisfied with mortality studies which predict survival well *beyond* the actual observation periods?
- Are we sure that resistance is not going to be a problem?
- How worried should we be about possible toxicity from life-long medication use?
- How do individuals with HIV “age”?
- What is the likelihood that a vaccine or cure will “change everything”?

So...
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The Aging HIV Patient

- First of all, this is a *good* thing!
- Definition of "older age": 50 yrs
- Observations: HAART -> decreased mortality, but increased…
  - Atherosclerosis
  - Dyslipidemia
  - DM
  - Loss of renal function
  - Osteopenia
  - Non-AIDS defining cancers
  - Neuro-cognitive changes

The (Prematurely?) Aging HIV Patient

- Potential explanations:
  - Accelerated immune senescence secondary to exhaustion of immunological resources
  - HAART toxicity
  - Accumulation of abnormal proteins
  - Chronic immune activation = inflammation

HIV and Risk of Atherosclerosis

Study	Findings
Role of Viral Replication, Antiretroviral Therapy, and Immunodeficiency in HIV-Associated Atherosclerosis Hsue, et al, AIDS: 2009 June 1; 23(9): 1059-1067	•Looked at carotid intima-medial thickness in HIV-, HIV+, and HIV+ "controllers" •IMT increased in anyone with HIV regardless of treatment status
Coronary Aging in HIV-Infected Patients Giovanni, et al, CID 2009:49 (1 Dec) HIV/AIDS	•Underwent coronary artery calcium scoring with CT •40% of HIV+ patients had increased scores •"Vascular age" increased by 15 years

Prospects for a Vaccine

- "Light at the end of the tunnel" – Dr. Fauci, 6/11
- RV144 trial – two vaccines in combination, 31% reduction in HIV infection (2009)
- Chimp (SIV) studies very successful
- Time to actual vaccine release…?

Dr. Anthony Fauci is Director of the National Institute of Allergy and Infectious Diseases

Prospects for a Cure

- Timothy Brown, “The Berlin Patient” – cured?

Mr. Brown's Cure

- Diagnosed HIV – 1995
- Diagnosed AML – 2006 (chemo->remission x 1 year)
- AML relapse – 2007 (chemo -> unsuccessful)
- Stem cell transplant – 2007
- AML recurred - 2008
- Second stem cell transplant – 2008
- Multiple complications for about 2 years
- 5-years post, no evidence of HIV, CD4 normal on no treatment....cured?

Prospects for a Cure

- "Infant Cured of HIV" 3/3/13
  - Infant born to HIV + mother
  - Early tests indicated infant infected with HIV
  - Started on intensive ART
  - Lost to follow up at 15 months
  - Returned off meds, but no evidence of active HIV
  - Cured?

HIV Cure

- "…I believe it's feasible." Dr. Fauci, 6/11
- After years of disappointment: real hope, new directions
- Functional vs. eradication cure
- "Elite controllers" – what do they teach us?
- Therapeutic vaccine combined with treatment -> eradication of virus?
- Time to cure…?

Modern-Underwriting - 2013

- 27 y/o male applies for $1,000,000 of permanent life
- Diagnosed with Stage 1 HIV two years ago by primary MD during recommended CDC screening
- Takes Atripla, once daily, otherwise healthy
- CD4 count is 745, viral load is undetectable
- Estimated life expectancy:
  - Possibly between 63 and 80 years
- Underwriting assessment:
  - Assess your products, business strategy, philosophy, and decide!

Wrap Up and Take Home

Dr. Z challenges you to…

- start a conversation – talk it up!
- think about what you already know and what more you *need* to know
- continue learning
- anticipate and embrace change in the coming years

THANK YOU!!!

Additional References

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