HIV In The Real World of Insurance

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HIV infecting a human T cell_National Institute of Allergy and Infectious Diseases-NIH

Can Prudential Offer Insurance?

- Effective Rx
- Industry studies and Munich Re work in S Africa
- Support goals of corporate responsibility and commitment to diversity
- Financial security for those living with HIV

- Not likely a money maker
- Marketing group ~150,000 with means and need for insurance
- Experimental - ?Claims results

Issues To Consider Outside Usual UW

- **State regulators**
  - “Are you going to take these people for a ride”
  - “Are you developing a new product to possibly discriminate against HIV + applicant?”
- **Marketing** - reputational risk
- **Confidentiality**
- **Brokers** - medically complex exclusions
- **Not BAU** - labor intensive with checks and balances

It Takes a Team

- Daily multi-disciplinary meeting for 6 months
- When to treat after dx was just becoming established
- Do we need to know all the meds?
- What is a significant variation in CD4 and viral loads?
- Pharmacy data base not 100% - good for compliance
- Records
- Employment - affordability

HIV - Where Are We Now

- Per the CDC, ~1.15 million people living with HIV in the U.S. by 2017, including 991,447 who have been diagnosed (up 100,000 since 2012)
  - Of those, it is estimated that half are under treatment and have achieved viral suppression
  - Largest increase in prevalence rates (56%) was among persons aged 65 years and older
- Reportedly 38,739 new HIV infections in the U.S. in 2017, down ~8% from 2012[1]

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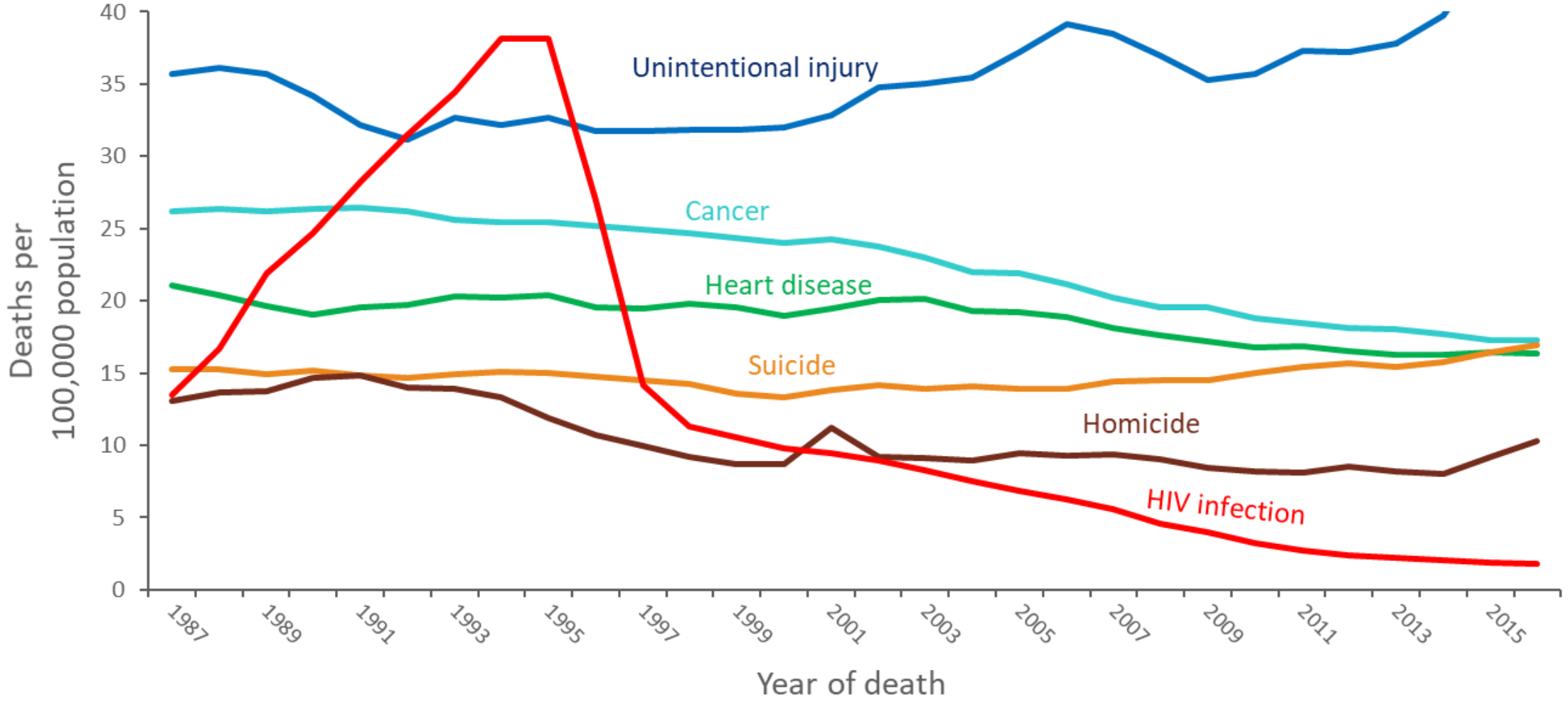
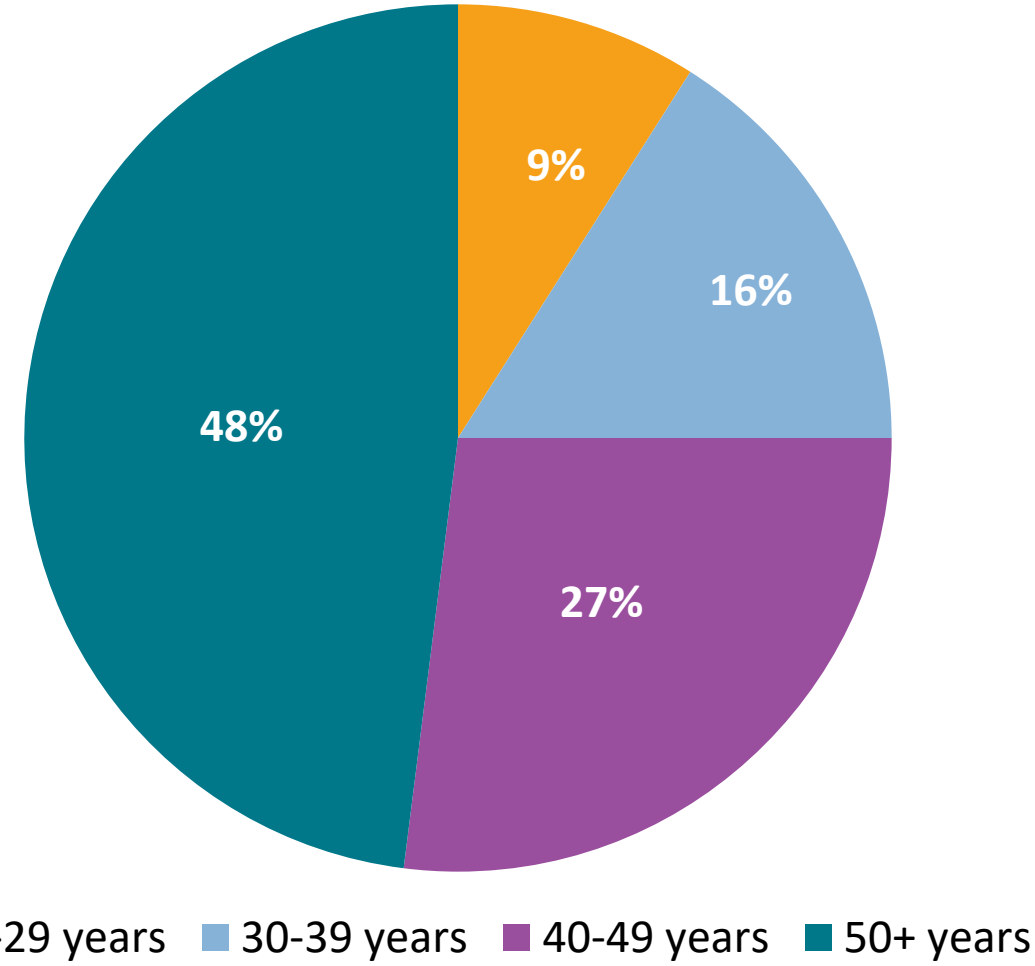
Trends in Annual Rates of Death due to the 6 Leading Causes among Persons 25–44 Years Old, 1987–2016 — United States

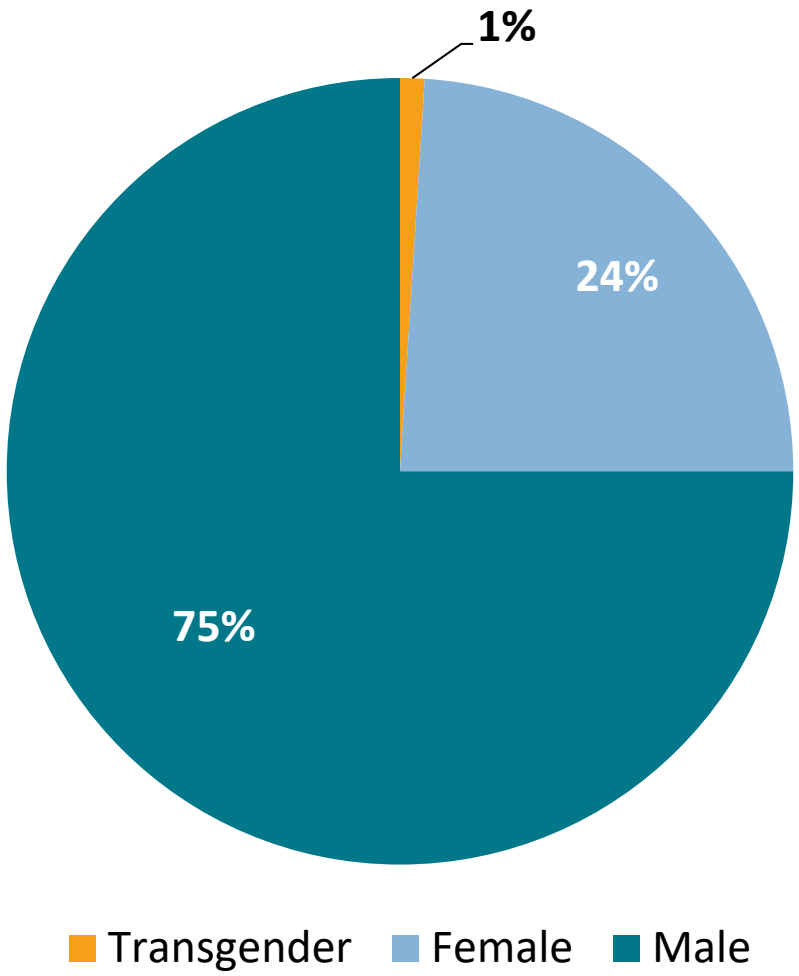


Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.

Adults with Diagnosed HIV by Age, 2015 Cycle



Adults with Diagnosed HIV by Gender, 2015 Cycle



Note: Transgender defined as those who self-identified as transgender or who reported a gender identity different from sex assigned at birth

Case 1 50 YO F

- Dx 2015 on ART triple therapy
- Unknown method of infection
- No history of AIDs defining condition

Date	CD4	VL
3/2019	Not done	<20
3/2018	628	<20
9/2017	742	<20
3/2017	589	<20
3/2016	499	102
10/2015	305	<20
7/2015	268	19,712

Mortality prognostic factors

Consistently identified

- CD4 counts – current and trends
- Viral load – current and past
- Age
- Duration of ART
- Concomitant Hep B or Hep C
- IV drug use history
- Interruptions in treatment

Associated – but an independent risk?

- Smoking
- STD history
- CD4/CD8 ratio
- Cumulative time at low CD4 counts
- Year of ART initiation
- Education level
- Anemia

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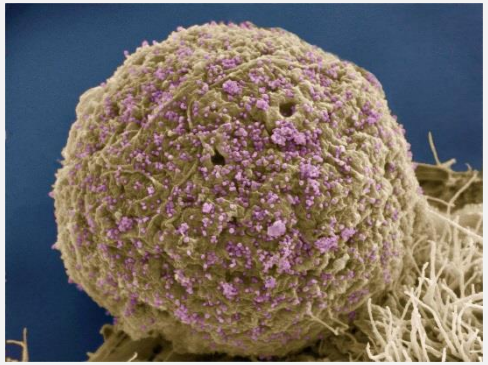
CD4 T-cell count

Reflects the current risk of acquiring opportunistic infections:

- Mean ~1000, range 500-2000 cells/μL, in uninfected
- Counts vary - serial measurements are useful
- A CD4 count below 200/μL is considered AIDS-defining in the US
- Stable CD4 counts >500 is especially favorable
- CD4 350-499 also fare well, and even 200-349 not ideal but many studies find risk to be only slightly worse then 350+ [2,3]



HIV_infected T-cell. Credit Mark Ellisman and Tom Deerinck, National Center for Microscopy and Imaging Research

CD4 count at diagnosis (baseline) is predictive of HIV infection duration:

- Estimated median 1.2 years from infection to CD4 <500, but range is wide [4]
- CD4 count at start of ART is a strong predictor of short-term mortality, but less so over time and probably not important after 3-5 years [5,6]

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HIV Viral load in peripheral blood

Surrogate marker of viral replication rate; not a diagnostic tool

With therapy, viral loads can often be suppressed to an undetectable level (< 20-75 copies/mL)

Related to rate of progression to AIDS and death

- Viral loads >30,000/μL are 18.5x more likely to die of AIDS than those with undetectable viral loads

Viremia “blips” can occur, typically < 400 copies/mL, but this is not thought to predict virologic failure (defined as a confirmed viral load of > 200 copies/mL)

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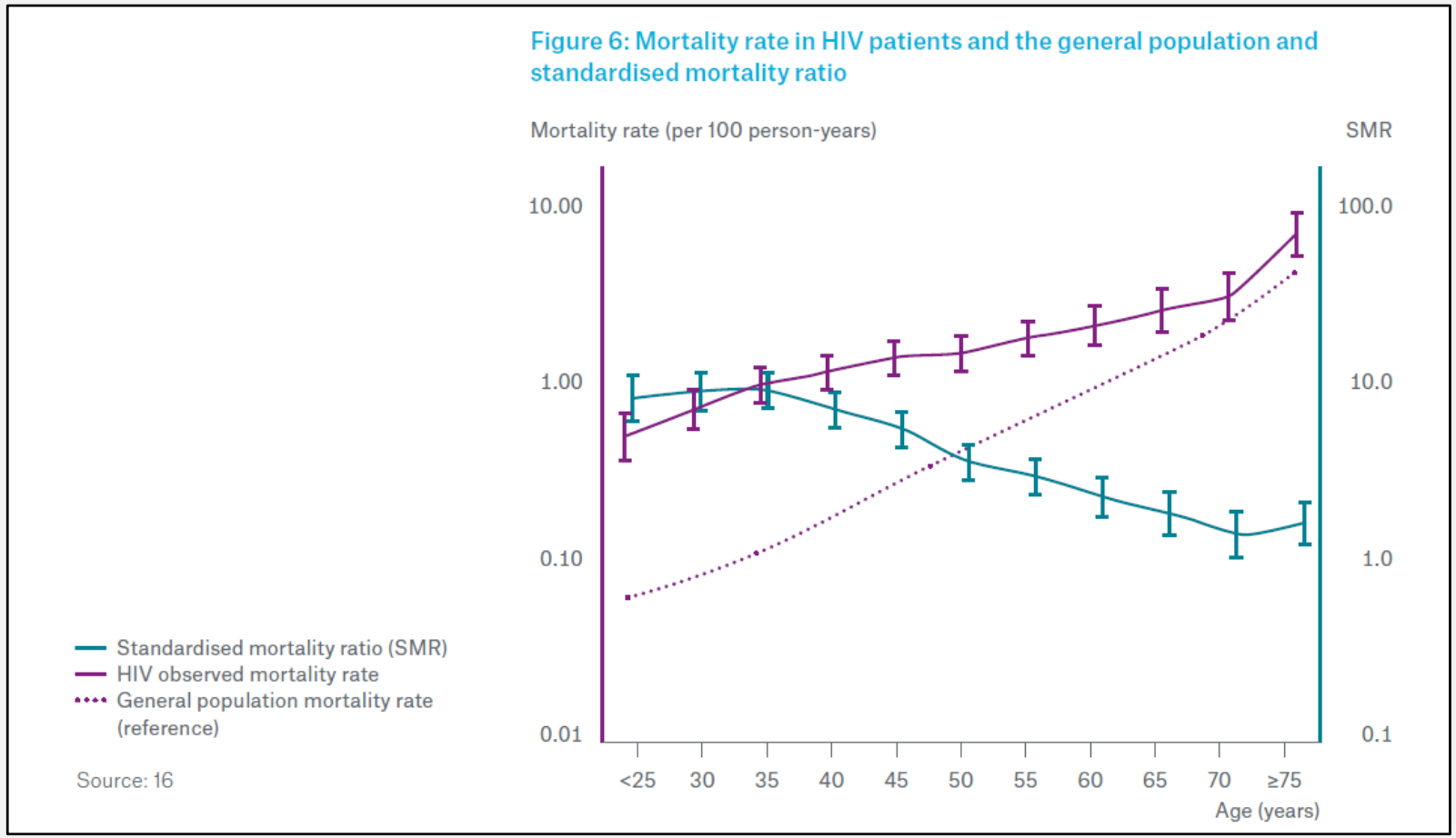
Additional prognostic factors – impact of age

- Mortality rates increase some with age but MRs drop significantly



Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.
All-cause mortality in treated HIV-infected adults with CD4 500/mm3 compared with the general population: evidence from a large European observational cohort collaboration. International Journal of Epidemiology 2012; 41: 433–445.

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Importance of treatment adherence

Higher mortality seen with:

- Interruptions in treatment [7]
- Cumulative time at low CD4 counts (e.g. <100 cells/µl) [8]

Both are likely markers of adherence to treatment, which could be related to:

- Health care access
- Treating facility
- Comorbid behavioral risks

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Additional prognostic factors

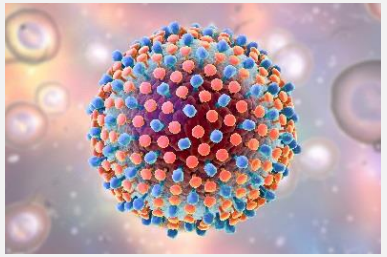
Duration of ART [3]

- Mortality is high during the first year, then levels off. MR probably stable after ~3 years.

AIDS defining illness history

Concomitant Hep B or Hep C

- Co-infection accelerates liver disease progression and may worsen HIV prognosis
- Not clear though if risk is more than additive [9,10]



iStock-612638916-hepatitis_c

IV drug use history [3]

- Both current and past use
- Likely comorbid risk with multiple other factors but even controlled for these still a significant factor

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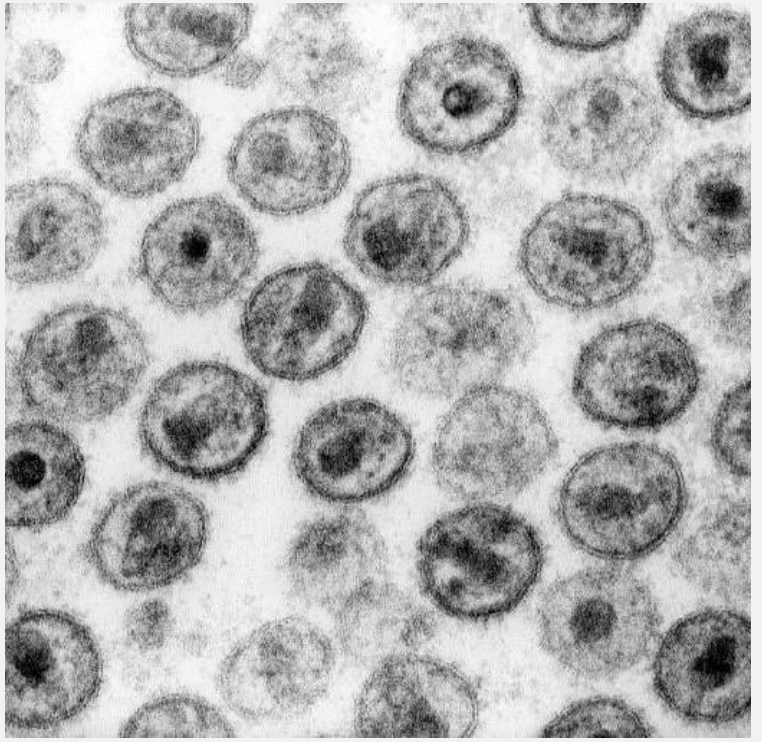
Prognostic factors in long treated HIV infection

After 10 years on ART (ART-CC cohort): [11]

- Low CD4 counts (but not CD4 count at ART initiation)
- Detectable viral load
- IV drug use transmission
- Prior AIDS-defining illness



Electron microscopy of human immunodeficiency virus (HIV)–1 virions. Courtesy of CDC (Dr Edwin P Ewing, Jr)

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Current understanding of HIV mortality risk

- Left untreated, the vast majority of people infected with HIV will progress to AIDS, although approximately 7% of those with HIV maintain an asymptomatic state, and about 1 in 300 are non-viremic "elite controllers."
- With proper treatment, many with HIV now have a relatively good 10-15 year prognosis
  - Select groups have a life expectancy similar to the general population
- Limited data beyond that point – some concerns for possible longer term risk, but just as much or more reason to predict newer treatments will lead to better outcomes.

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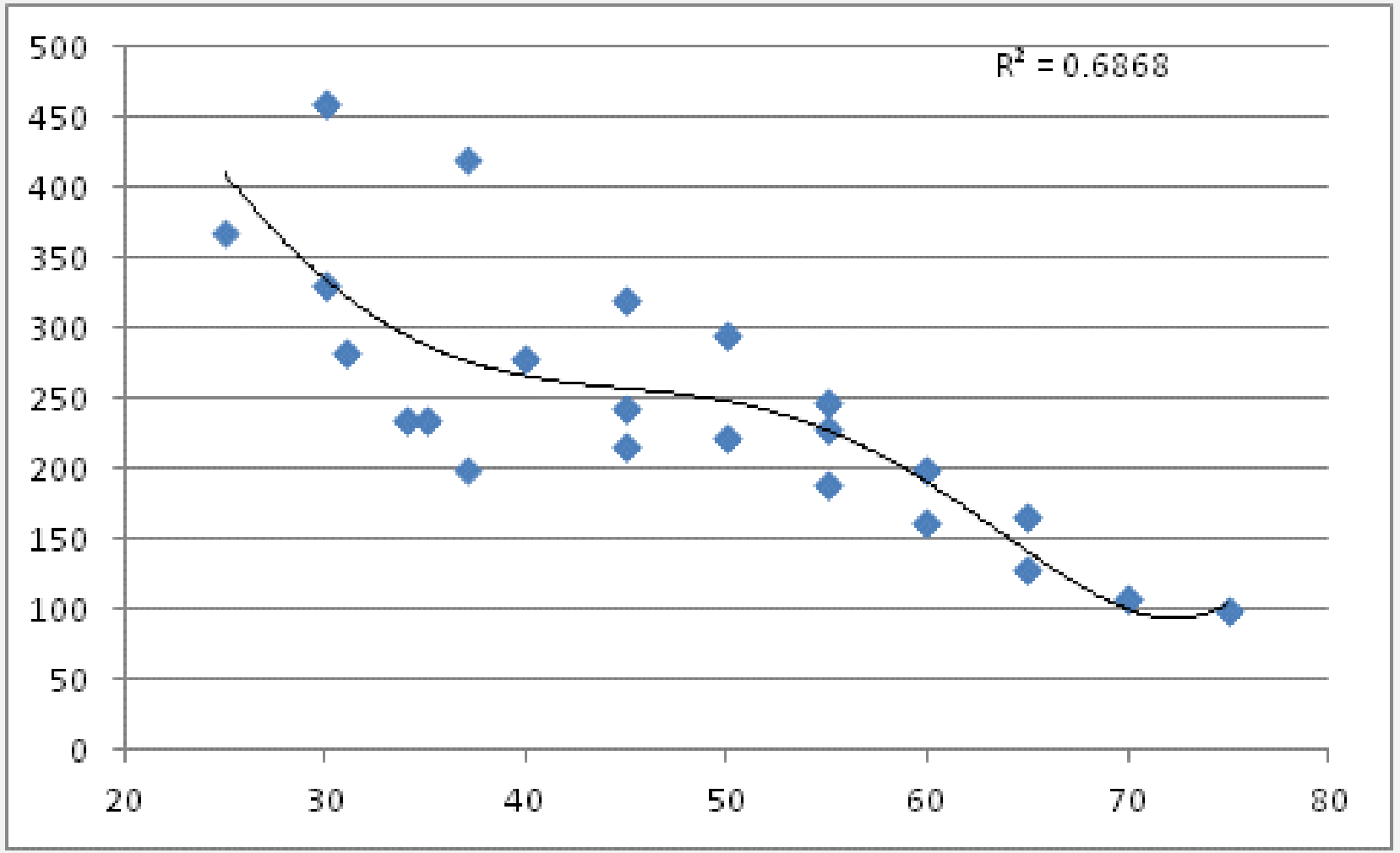
HIV Mortality – Overall composite of data analysis



Summary data
Dr. Robert Lund

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Calculated MRs – European and South African analysis

With viral suppression and no adverse prognostic factors (unisex MR)

Blended ART-CC and South African dataset 2015; Sarkin, et al, MunichRe

Current CD 4			
<200			
All ages		564	Dec
200-349			
<30 at application		290	300
30-39		197	200
40-49		80	75
50-59		45	50
60+		15	25
350-499			
<30 at application		218	225
30-39		148	150
40-49		61	50
50-59		34	25
60+		11	0
>500			
<30 at application		169	175
30-39		115	125
40-49		47	50
50-59		26	25
60+		9	0

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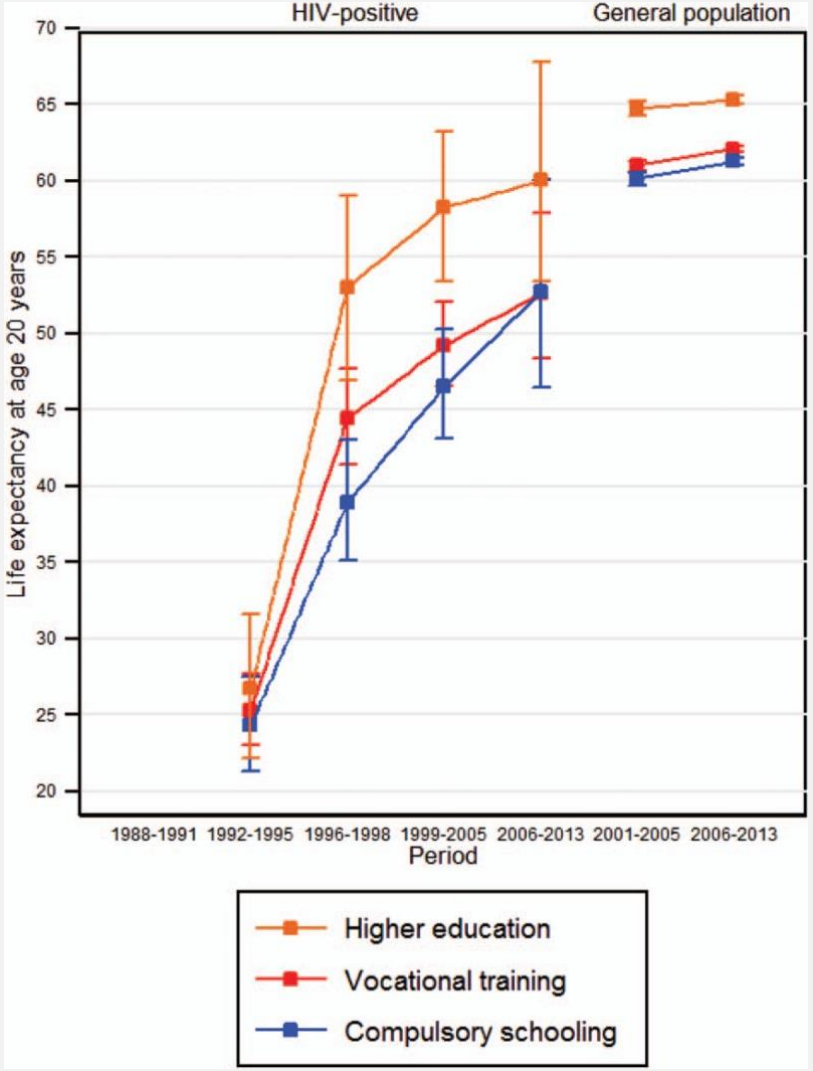
Life expectancy at age 20 years by education



Swiss HIV Cohort Study

Estimated LE from dual therapy (1992–1995) to recent combination ART era (2006–2013), and in a matched sample from the general Swiss population (2001–2013) [6]

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Is the favorable prognosis durable?

- Studies that focus on current CD4 counts found short-term mortality to be increased by factors of 1-1.5 and 1.8-2 for current counts of >500 cells/µl and 350–499 cells/µl, respectively, compared to the general population [2,3,12,13]
- MunichRe data show that the observed mortality ratios were stable within the first ten years of treatment and longer

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Percent 5-year risk of death (95% CI) from 10 years after start of ART, by age

Virologically suppressed, No IV drug use, No AIDS [14]

- 13,011 patients during follow-up from 10 years after starting ART, median age 46, 80% male
  - Median CD4 count was 250 cells/μL at ART start and increased to 550 at ten years (81% ≥350)
  - 88% had HIV-1 RNA <200 copies/mL at ten years
- IDU transmission, AIDS diagnosis, and low CD4 count and/or detectable viral replication ten years after starting ART were associated with higher subsequent mortality, but not CD4 count at ART onset
- Main causes of death were non-AIDS cancer [25%], AIDS [19%]), cardiovascular [12%], and liver-related [10%]

CD4	0-99	100-199	200-349	350-499	500-749	≥750	Gen pop. (Fr)
Age 16–39:	6.9 (4.9–9.8)	3.9 (2.7–5.5)	2.2 (1.6–3)	1.7 (1.2–2.3)	1.2 (0.9–1.6)	1.2 (0.8–1.6)	0.3
Age 40–49:	10.9 (8.2–14.3)	6.1 (4.6–8.1)	3.5 (2.7–4.4)	2.7 (2.1–3.4)	1.9 (1.5–2.4)	1.9 (1.5–2.4)	1.0
Age 50–59:	18.8 (14.3–24.4)	10.8 (8.2–14.2)	6.1 (4.8–7.8)	4.8 (3.8–6)	3.4 (2.7–4.3)	3.3 (2.6–4.3)	2.5
Age 60+:	36.4 (28.2–46.2)	22.1 (16.9–28.5)	12.9 (10.3–16.2)	10.1 (8.1–12.7)	7.2 (5.7–9.1)	7.1 (5.5–9.1)	5.8

Trickey A, May MT, Vehreschild J, et al. *Cause-Specific Mortality in HIV-Positive Patients Who Survived Ten Years after Starting Antiretroviral Therapy.* PLOS ONE | DOI:10.1371/journal.pone.0160460 August 15, 2016

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Case 1 50 YO F

Munich RE

- Dx 2015 on ART triple therapy
- Unknown method of infection
- No history of AIDs defining condition
- Good follow-up but last CD4 check 3/18

Date	CD4	VL
3/2019	Not done	<20
3/2018	628	<20
9/2017	742	<20
3/2017	589	<20
3/2016	499	102
10/2015	305	<20
7/2015	268	19,712

Laboratory Test	Timepoint or Frequency of Testing					
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months
HIV Serology	√ If HIV diagnosis has not been confirmed					
CD4 Count	√	√		√ During first 2 years of ART, or if viremia develops while patient is on ART, or CD4 count <300 cells/mm³		√ After 2 Years on ART with Consistently Suppressed Viral Load: *CD4 Count 300–500 Cells/mm³:* • Every 12 months *CD4 Count >500 Cells/mm³:* • CD4 monitoring is optional
HIV Viral Load	√	√	√[d]	√[e]	√[e]	

More Unique UW Aspects

- CD4 and viral load up or down trends-like PSA
- Viral Aquistion-usually not known
- CD4/CD8 ratio
- STD's-gonoccal, chlamydia syphillis
- Medication changes
- Adherence to appts and follow up for abnormal tests
- Medication compliance
- ETOH or drug abuse
- Anal dysplasia
- Anemia
- Glucose intolerance?

UW Applicants Ideal Applicant

- Pre-screened
- Single provider with excellent documentation
- Good track record of compliance
- CD4 consistently >500 and viral load undetectable
- Non-smoker
- No substance abuse
- No Psych issues
- Few STDs
- No hx of Hepatitis or IV drug use

Case 2 49 YO M

Munich RE

- HIV dx 2011, non-compliant with ART until 2014 - multiple missed doses
  - CD4 count >500 since 2014 and viral load suppressed
  - Hep B and C neg, RPR neg
- OSA, Ca score 85 (89%), Depression
- App stated non smoker - IRP +Nicotine
- Recent STD (GC-urethra)

Associated factors – but an independent risk?

Smoking

STD history

Cardiac risk

Depression

Education level

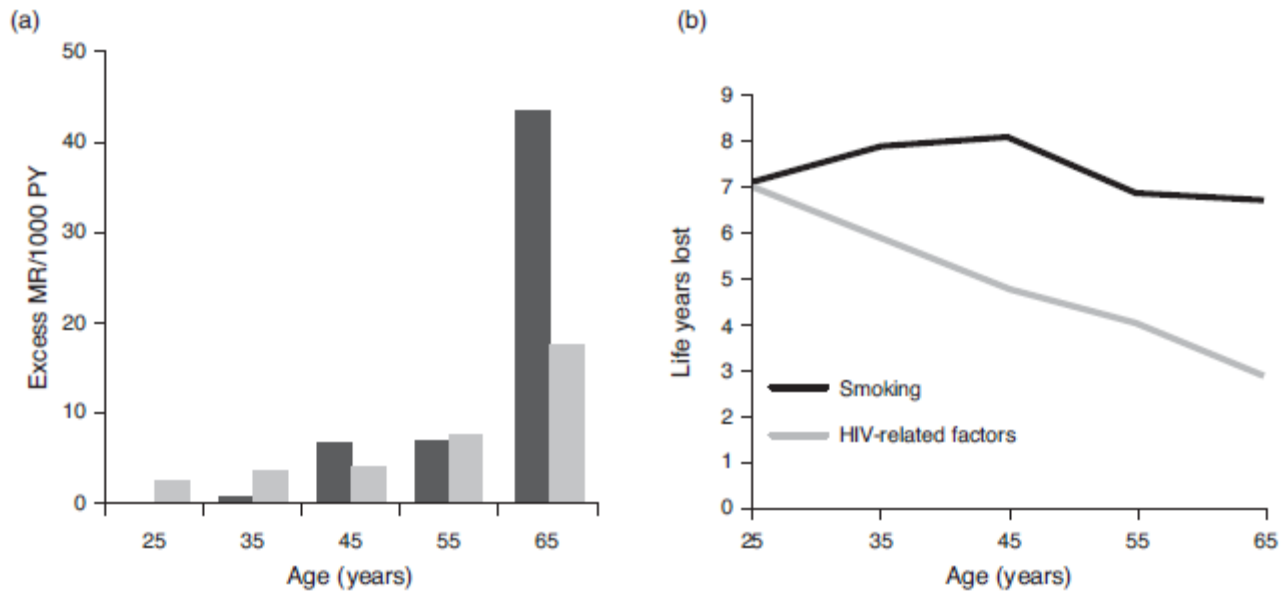
Comorbid Smoking Risk

Tobacco smoking is higher amongst HIV-infected persons

- Kaiser study comparing HIV infected to non-infected HIV patients:
- more likely smoking (45.2% vs. 31.1%)
- drug/alcohol abuse (20.6% vs. 8.6%)
- HBV or HCV infection (11.5% vs. 1.7%) [15]

- Swiss cohort, 41% current and 16% former smokers: MRs 2.20 and 1.15 compared to never smokers [6]

Smoking and Life expectancy among HIV infected



Smokers 2 fold increase in mortality, 1/3 of smokers from lung cancer. Life expectancy average of 8 years less

Helleberg M et al, AIDS 2015; 29:221 [16]

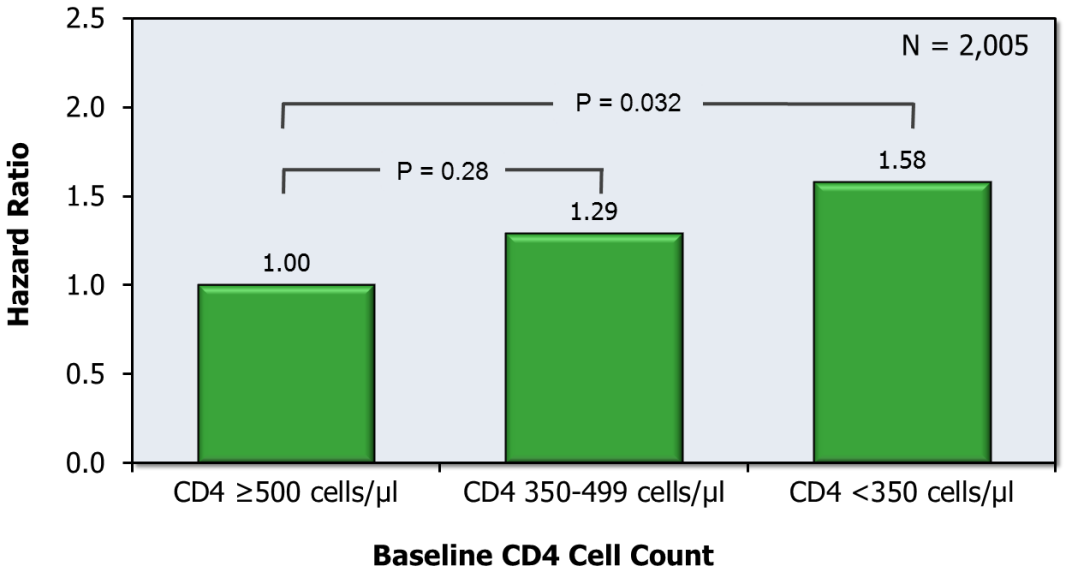
STDs - Added Risk if Treated for HIV?

- Limited outcome data
- U.S. military study found an STD history did not impact mortality (RR 1.0) [17]
- Potential concerns include:
  - Possible marker of other behavioral risks
  - Direct risk from the STD (syphilis, hepatitis B and C)
  - Increased risk of HPV-related malignancy
  - Risk of acquiring different HIV strains (and higher risk of Rx resistance?)

- More of a red flag than an absolute contraindication?

Baseline CD4 Count Associated with Cardiovascular Disease Events: HIV Out Patient Study (HOPS)

Cox Proportional Hazard: Relationship of Baseline CD4 and Risk of Subsequent Cardiovascular Events

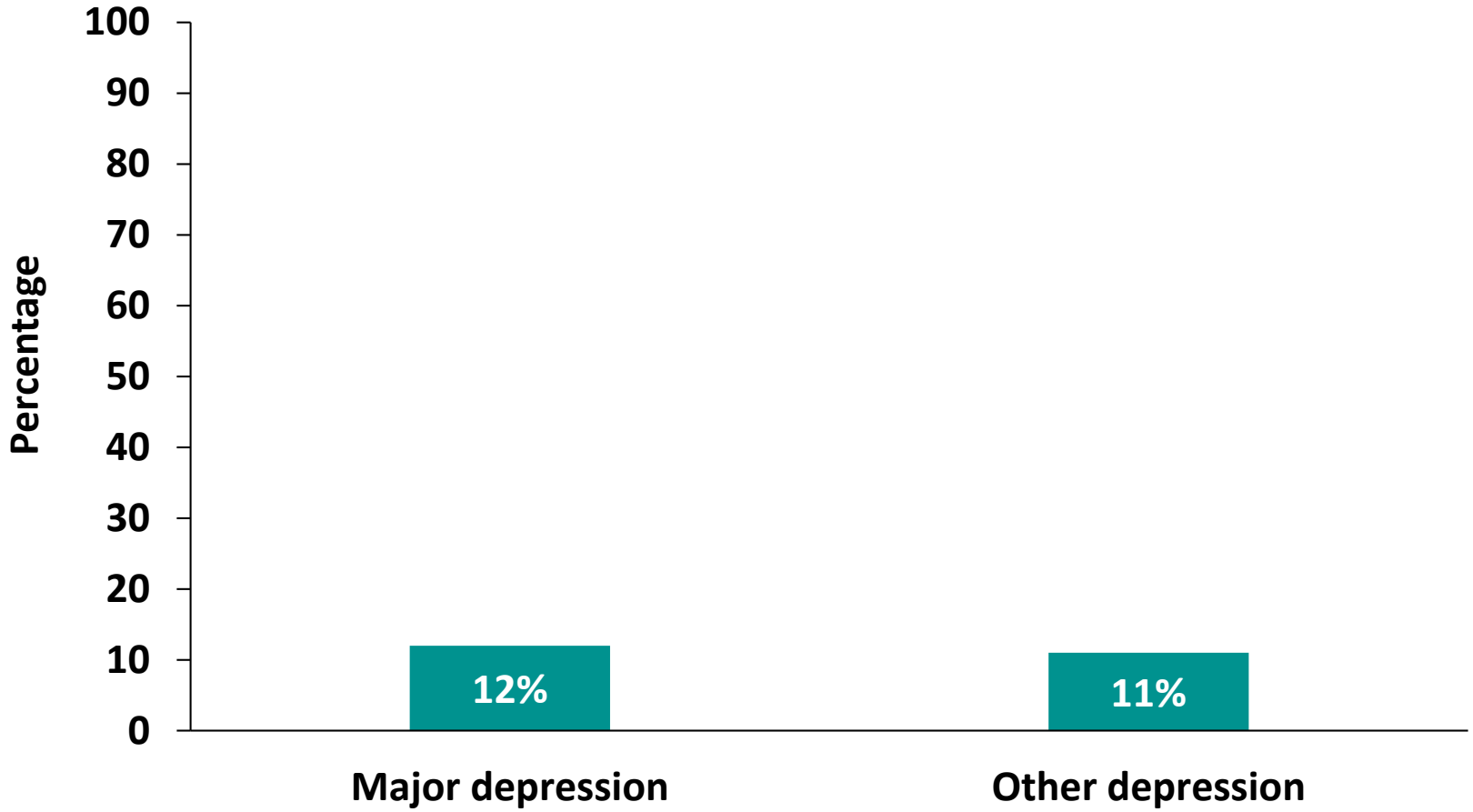


- Even after accounting for established risk factors, HIV+ individuals have 50%–75% greater risk of acute MI than demographically similar uninfected individuals

Freiberg MS JAMA Intern Med 2013; 173:614

Source: Lichtenstein KA, et al. *Clinical Infectious Diseases*. 2010;51:435-447.

Depression[a] among Adults Receiving HIV Medical Care, 2015 Cycle



[a] Assessed for the past 2 weeks; responses to the 8 items on the Patient Health Questionnaire (PHQ-8) were used to define "major depression" and "other depression," according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV-TR)

Adherence to Antiretroviral Therapy (ART) among Adults with Diagnosed HIV taking ART, 2015 Cycle

	%	95% CI
Took 100% of prescribed ART doses in past 30 days	60	(57-62)
How well did you do at taking your HIV medicines in the way you were supposed to?		
Very poor	1	(1-2)
Poor	2	(1-2)
Fair	5	(4-6)
Good	12	(11-13)
Very good	26	(24-28)
Excellent	54	(51-56)
How often did you take your HIV medicines in the way you were supposed to?		
Never	1	(1-2)
Rarely	1	(1-1)
Sometimes	2	(1-2)
Usually	5	(4-6)
Almost always	23	(21-25)
Always	69	(67-70)

Reasons[a] for Last Missed Antiretroviral Therapy (ART) Dose among Adults with Diagnosed HIV taking ART, 2015 Cycle

	%	95% CI
Forgot to take	37	(34-39)
Change in your daily routine or were out of town	25	(23-28)
Fell asleep early or overslept	20	(18-22)
Had a problem getting a prescription, a refill, insurance coverage, or paying for HIV medicines	15	(13-17)
Felt depressed or overwhelmed	10	(9-12)
Did not feel like taking HIV medicines	8	(7-8)
Had side effects from your HIV medicines	7	(6-8)
In the hospital or too sick to take HIV medicine	7	(5-8)
Was drinking or using drugs	6	(4-8)

[a] Participants may report more than one reason for last missed dose

Prudential Approved Applicants

- Pre-qualification
  - Age 30-60
  - > 6 months since current ART
  - Viral load undetectable C>500
  - No Hx of prior AIDS defining condition
  - Virus acquisition not via blood transfusion or IV drug abuse
  - HCV and HBV neg
  - Compliant
- Acceptance rate on program
  - 17% approved and 62% declined
  - 79 % of those approved accepted
- Average age 47 and average Face 1.4 million

What Does the Future Hold

- Berlin and London patients
  - Received stem cell transplants from donors with two genetic mutations that remove the CCR5 receptor from the surface of the CD4 T-cell
  - Without that receptor, most HIV strains can't gain access to the cell and can't spread
  - Precision medicine - uses lentiviral vectors and nucleases to target ablation or down-regulation of CCR5 expression
- Entry and fusion inhibitors (e.g. PRO140) – investigative monoclonal Ab directed against the host's CD4 cell surface receptor, blocking HIV entry into cells
  - UB-421: Monotherapy maintained suppression of plasma viremia in the absence of ART for 8-16 weeks
- Immunotherapy – targeted therapies to open up the HIV-1 envelope protein to allow one’s own immune response to react
- Vaccines – RV144 trial in Thailand showed modest protection (31%), but progress is being made

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Questions to answer for the future of HIV treatment

- Current Integrases Inhibitor-based Rx regimens more effective than prior ART?
- How frequent is anti-retroviral drug resistance?
- Accelerated aging from chronic immune stimulation?
  - Age advancement found to be related to persistent CMV or HepB infection, prior immunodeficiency, and cumulative saquinavir exposure
- Two drug ART now available. Injectables and Implantables?
- Cures?
  - HIV-1 provirus integrates into host cell leaving an important reservoir – how can it be reached?

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CRISPr gene editing to snip out HIV genome

Scientists at Lewis Katz School of Medicine at Temple University Eliminate HIV-1 from Genome of Human T-Cells

POSTED ON MARCH 21, 2016

A specialized gene editing system designed by scientists at the Lewis Katz School of Medicine at Temple University is paving the way to an eventual cure for patients infected with HIV, the virus that causes AIDS. In a study published online this month in the Nature journal, *Scientific Reports*, the researchers show that they can both effectively and safely eliminate the virus from the DNA of human cells grown in culture.

According to senior investigator on the new study, **Kamel Khalili, PhD**, Laura H. Carnell Professor and Chair of the Department of Neuroscience, Director of the Center for Neurovirology, and Director of the Comprehensive NeuroAIDS Center at the Lewis Katz School of Medicine at Temple University (LKSOM), "Antiretroviral drugs are very good at controlling HIV infection. But patients on antiretroviral therapy who stop taking the drugs suffer a rapid rebound in HIV replication." The presence of numerous copies of HIV weakens the immune system and eventually causes acquired immune deficiency syndrome, or AIDS.

Curing HIV/AIDS – which has claimed the lives of more than 25 million people since it was first discovered in the 1980s – is the ultimate goal in HIV research. But eliminating the virus after it has become integrated into CD4+ T-cells, the cells primarily infected with HIV, has proven difficult. Recent attempts have focused on intentionally reactivating HIV, aiming to stimulate a robust immune response capable of eradicating the virus from infected cells. However, to date, none of these "shock and kill" approaches has been successful.

Dr. Khalili and colleagues decided to try a different approach, specifically targeting HIV-1 proviral DNA (the integrated viral genome) using uniquely tailored gene editing technology. Their system includes a guide RNA that specifically locates HIV-1 DNA in the T-cell genome, and a nuclease enzyme, which cuts the strands of T-cell DNA. Once the nuclease has edited out the HIV-1 DNA sequence, the loose ends of the genome are reunited by the cell's own DNA repair machinery.

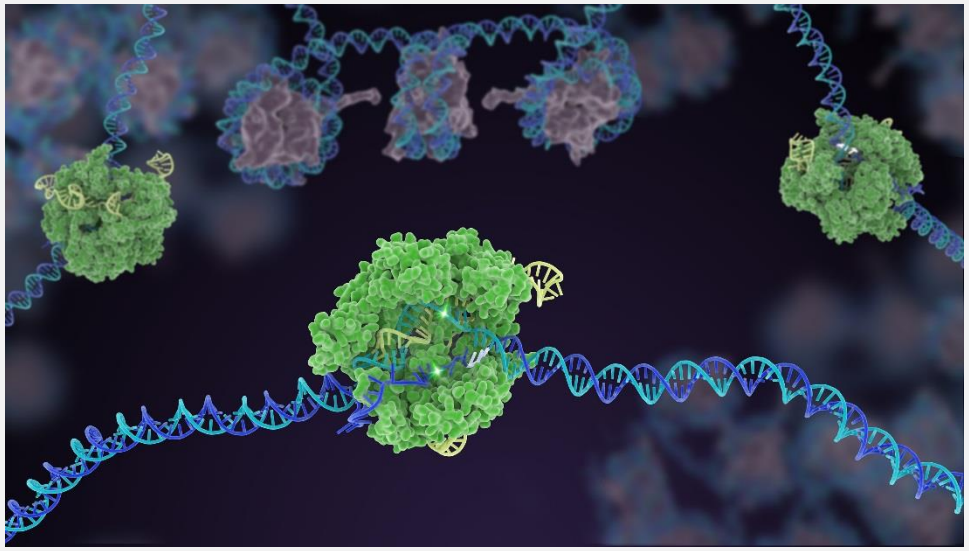

Image courtesy Janet Iwasa for the Innovative Genomics Institute at UC Berkeley

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Discussion

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HIV on Bridges Between Infected Immune Cell and Uninfected Brain Cell

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