HIV Panel Discussion

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HIV Epidemiology

- 36.9 million people living with HIV worldwide with 2.1 million new infections and ~1.5 million related deaths in 2014 (UNAIDS)
  - 15 million are on ART
  - 70% are in Sub-Saharan Africa
- Prevalence in U.S.: Estimated 1.2 million (CDC 2013)
  - 13% unaware of diagnosis
  - 39% engaged in HIV care
  - 30% achieved viral suppression (~368,000)
- Mode of transmission for new infections (U.S. 2010): 65% MSM, 25% Heterosexual, and 7% IV drug use
- 20% of new infections are in women, 24% presented with AIDS, and 18% are now in those ≥50 years of age
- Now estimated that half of those living with HIV are >50 yrs
Timeline of HIV

- **1900s**: HIV thought to have spread to humans from chimpanzees (bush meat trade in central Africa)
- **1959**: First known death from HIV in the Congo
- **1981**: MMWR report - 5 cases of PCP; syndrome of AIDS described
- **1983**: HIV isolated
- **1985**: Commercial antibody testing becomes available
- **1986**: Treatment consists primarily of managing the complications of AIDS
Life Insurance Industry Reaction

1987 SOA AIDS Task Force

- Time from 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
- Predicted in excess of $30 billion in claims by the year 2000!

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<tr>
<th>Main Concerns and Actions Taken</th>
<th>Business “on the books”</th>
<th>New Business</th>
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<td>Creation of AIDS reserves</td>
<td>Testing – antibody vs. other surrogate tests</td>
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<td>Adjustment of premiums</td>
<td>Stopped writing policies in certain jurisdictions</td>
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Timeline of HIV (continued)

- 1987: Zidovudine (AZT) approved
- 1992: Multidrug anti-retroviral therapy available
- 1996: Triple therapy introduced (HAART) after the discovery of the protease inhibitor ritonavir
- 2006: Atripla™ (efavirenz/emtricitabine/tenofovir) approved – once a day dosing
- 2012: OTC 20-min home HIV test released
- 2013: Truvada™ (tenofovir + emtricitabine) advised for PrEP
2015 HIV Treatment

• ART: Now >25 drugs in 6 major classes
  — Backbone of two NRTI’s (nucleoside reverse transcriptase inhibitors)
  — A third drug of a different class such as NNRTI (non-nucleoside RTI), PI (protease inhibitor), Integrase Strand TI, or CCR5 antagonist

• Goals: suppress viral replication, restore immune function (CD4 count), prevent transmission, prevent drug resistance, improve QOL and longevity
Case #1

• 42 yr old female, Zimbabwean immigrant to New Zealand found HIV positive on immigration blood test 2005
• Earlier details not known, TB treated in 2004, HCV negative, 12 year old daughter HIV negative
• Reportedly very compliant; some adjustments to ART in 2005, but now stable on Efavirenz™ (Sustiva) since 2007
• Current CD4 cell count 557/mm3
• Viral load undetectable until 2011 when it was minimally detectable at 1.73 log10 copies/mL (54 copies/mL)
• This was considered to be a "blip" given her otherwise excellent prognostic factors
• LFTs slightly abnormal – felt to be due to treatment
Swiss HIV Cohort Study 2004

• 10,977 HIV patients followed for median of 46 months
• Standardized mortality ratios (SMRs) calculated, unadjusted for any co-morbid features
• SMR decreased from 79.3 in the pre-HAART era to 15.3 in the HAART era
• Best case HAART era SMRs were 5.2 for men
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<th>Study and Year</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
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<td><strong>COHERE cohort 2012</strong></td>
<td>80,642 individuals from 31 European countries starting ART 1998-2008 and having a CD4+ measurement within 6 months.</td>
<td>Among 35,316 non-IVDU individuals with CD4+ counts &gt;500, SMR was 0.9 for men and, after at least 3 years of ART, was 1.1 in women.</td>
<td>Large cohort allowed for extensive data analysis, such as considering those with prolonged maintenance of favorable CD4+ counts.</td>
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<td><strong>Continuous antiretroviral therapy arms of the SMART and ESPRIT trials 2013</strong></td>
<td>Prospective cohort of 3280 individuals age 20-70 (12,357 person-years of follow-up). 53% from N. America. Excluded those with IVDU.</td>
<td>SMR compared to general population was 1.0 (CI 0.69-1.30) for those with CD4+ counts &gt;500 and viral suppression at last follow-up. It was 1.77 (CI 1.17-2.55) for those with CD4+ counts of 350-499.</td>
<td>Had excellent ascertainment of vital status (a limitation of many studies). Overall mortality 5.0/1000 person-years. Only 3.2% of deaths were felt to be due to AIDS.</td>
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<td><strong>NA-ACCORD cohort 2013</strong></td>
<td>22,937 participants from the North American AIDS Cohort Collaboration on Research and Design age 20 and up, on ART, and with a CD4+ count within 6 months on ART.</td>
<td>Projected weighted life-expectancy at age 20 was calculated to be 42.7 yrs for the overall group, 57.3 yrs selected only by MSM transmission, and 54.6 yrs by CD4+ count ≥350 only, compared to 59.7 yrs in Canada and 57.0 yrs in the U.S. general population.</td>
<td>The overall unweighted mortality rate was reported as 19.8/1000; 12.5/1000 in MSM transmission, and 11.3/1000 in CD4+ &gt;350 group (which appears possibly counter to the projected LEs).</td>
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<td><strong>UK-CHIC Study 2014</strong></td>
<td>21,388 HIV+ individuals receiving care in the UK 2000 to 2012.</td>
<td>After 5 years on ART, expected age at death of 35 year-old men varied from 54 to 80 for those with CD4+ counts &lt;200 and no viral suppression versus CD4+ ≥350 and viral load suppressed.</td>
<td>Article specifically states that their study supports “that patients successfully treated with ART should be eligible for life insurance.”</td>
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<td><strong>Multicenter AIDS Cohort (MACS) and Women’s Interagency HIV Study (WIHS) 2014</strong></td>
<td>U.S. population cohorts. Compared mortality rates between the HIV-negative members and the HIV-positive members on ART. Median follow-up 10.2 years.</td>
<td>Median life expectancy of HIV+ group starting ART when their CD4+ counts were ≥350 was 72, compared to 69 if counts were 201-350, 66 if 200 or less, and compared to 75 in the HIV-uninfected group.</td>
<td>In these socially matched groups, rates of non-AIDS deaths were the same in those starting ART with CD4+ counts ≥350 and those who were HIV-negative.</td>
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Insurability of HIV positive people treated with antiretroviral therapy in Europe

• Collaborative analysis of the ART-CC cohort 2013
• 34,680 patients who were not infected via IVDU, were Hep C negative, and started ART 1996 to 2008. Followed for 174,906 person-years.
• Sub-groups at older ages and longer ART duration had more favorable mortality ratios
  – E.g., MR compared to insured lives was 165% for those age 40-49 who started ART after 2000, had no ADI, had 6 month CD4+ counts >350 and HIV RNA <10,000, and were on ART for 7+ years.
• 68% of study group had MR estimated at ≤500%
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Case #2

- HIV pos identified June 2012
  - On ART since 2012: NORVIR™ (ritonavir), PRELISTA™, TRUVADA™, (tenofovir + emtricitabine), ATRIPLA™ (efavirenz/emtricitabine/tenofovir
- Regular monitoring at 6 month intervals
  - Serial CD4 cell counts: 250, 279, 223/mm3
- Last seen Sept 2014:
  - CD4 cell count 250/mm3
  - Viral load not detectable (<50 copies/mL)
  - HCV serology negative
- No information as to mode of acquisition, no indication of an ADI
Insurability of HIV positive people treated with ART

AIDS. 2013 Jun 19;27(10):1641-55

Percentage relative mortality compared with HIV-negative insured lives (actual/expected claims ratio) of HIV-positive people according to CD4 cell count 6 months after start of ART, duration of ART, age group and calendar period of initiation of ART, among individuals without an AIDS diagnosis and with 6-month HIV-1 RNA less than 1000 copies/ml and in countries other than the Netherlands.
Case #3

• 27 year old male; seeking Life, Disability, and Critical Illness coverage
• In a same-sex marriage -- states that he uses Truvada as an HIV preventative, as part of a 'safe-sex practice'
• No other meds or medical history
• Lab all normal and HIV negative
### European Truvada (PreP) Studies

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<th>Country</th>
<th>Protocol</th>
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<td>PROUD, 2015</td>
<td>UK</td>
<td>Daily dosing</td>
<td>Reduced risk by 86%</td>
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<tr>
<td>IPERGAY, 2015</td>
<td>France</td>
<td>Intermittent dosing</td>
<td>Reduced risk by 86%</td>
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Case #4

• 44 year old male - application date January 2014
• BMI 21.6 - Smoker (10 cigarettes/day)
• AIDS CDC stage C diagnosed in May 2012
  – Pneumocystis jiroveci pneumonia (PJP; formerly known as Pneumocystis carinii pneumonia, PCP)
  – Candida esophagitis
• APS: 10 days in hospital in June 2012 for Staphylococcus aureus pneumonia
• Well followed since, on combination anti-retroviral therapy (cART)
  – ISENTRESS™ (raltegravir) & TRUVADA™ (tenofovir + emtricitabine) May 2012 – Feb 2013 (renal side effects)
  – EVIPLERA (emtricitabine, rilpivirine, tenofovir) Feb 2013 to present
• Recent Viral load undetectable, CD4 cell count 686/mm³
Survival of Danish HIV-infected persons aged 25-65 who started ART Jan 1, 1998 – July 1, 2009 compared to comparison cohort without health issues (Group 0)

Figure 1. Cumulative survival for HIV-infected patients starting ART and persons from the general population. Time was calculated from 1 year after start of ART. The study population was categorized as: Group 0: Population comparison cohort (dotted line, N = 9,068). Group 1: HIV-infected patients without HIV risk factors, comorbidity or alcohol/drug abuse (N = 871). Group 2: HIV-infected patients with HIV risk factors, but no comorbidity or alcohol/drug abuse (N = 704). Group 3: HIV-infected patients with comorbidity, but no alcohol/drug abuse (N = 379). Group 4: HIV infected patients with alcohol/drug abuse (N = 313).

HIV risk factors: detectable viral load (>49 copies/ml) and/or CD4 below 200 cells/ul at the last measurement and/or AIDS-defining disease as of the index date. Comorbidity: diagnosed with comorbidity as defined in the Charlson Comorbidity Index before index date. Abuse: diagnosed with drug or alcohol abuse before index date or reporting drug abuse as route of HIV transmission.

doi:10.1371/journal.pone.0022698.g001
Kaplan-Meier curve showing survival by age, stratified by human immunodeficiency virus and smoking status for all study subjects (A).


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Lifecycle of the HIV Virus

1. Fusion of HIV to the host cell surface.
2. HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.
3. Viral DNA is formed by reverse transcription.
4. Viral DNA is transported across the nucleus and integrates into the host DNA.
5. New viral RNA is used as genomic RNA and to make viral proteins.
6. New viral RNA and proteins move to the cell surface and a new, immature, HIV forms.
7. The virus matures by protease releasing individual HIV proteins.

Host Cell

Preintegration complex

Mature Virion

Lytic Cycle of HIV

National Institute of Allergy and Infectious Diseases
Bibliography