“Towards an HIV Cure”
Entering the 4th decade

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4/30/13
Towards an HIV cure: a global scientific strategy

The International AIDS Society Scientific Working Group on HIV Cure
Outline

- HIV Epidemiology
- Treatment of HIV
- Preventing transmission
- Vaccines
- HIV cure research
AIDS—A Recent Viral Success

Many newly recognized/emerging infections since mid 1970s

- HCV, HTLV-1, Hantavirus, SARS, Helicobacter, Bartonella, Ebola virus, Legionnaire’s disease...

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

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient’s condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.
AIDS—A Recent Viral Success

- **Virus isolated 1983**, blood testing 1985
- First known human sample from a man from Democratic Rep of the Congo 1959
- Arose in humans in early 20th century via transfer from chimpanzees
- Since first recognized human case, has infected > 60 million with > 30 million deaths

Adults and children estimated to be living with HIV, 2011
By WHO region

Number of people (millions), by WHO region

- Eastern Mediterranean: 0.56 [0.41-0.80]
- Western Pacific: 1.30 [1.10-1.60]
- Europe: 2.30 [2.00-2.70]
- Americas: 3.00 [2.50-3.70]
- South-East Asia: 3.5 [2.60-4.60]
- Africa: 23.00 [22.00-25.00]

Total: 34.00 [31.40-35.90]
Adult HIV prevalence (15-49 years), 2011
By WHO region

Global prevalence: 0.8% [0.7-0.8]
Good News

- Rate of new HIV infections is falling globally
  - ↓ 50% in 25 countries from 2001 → 2011
- In the past two years there has been a 60% increase in the number of people accessing treatment—8 million people are on antiretroviral therapy (ART)
- Death rate from AIDS has decreased significantly in Africa

UN World AIDS Day Report 2012; De Cock, Emerg Infect Dis 2011 17:1044
Bad News

- Need for HIV medications is 14.8 million persons
- Only 50% of infected persons worldwide know their HIV status
- Focal significant increases in new HIV infections over the last decade
  - Bangladesh, Indonesia, Philippines, Sri Lanka
  - Middle East and North Africa
  - Eastern Europe and Central Asia
  - MSM since 2010

2.7 million new infections in 2011

UN World AIDS Day Report 2012
Prevalence of HIV infection within some US populations rivals that in some sub-Saharan African countries.
US HIV Statistics

US HIV Statistics

CDC reports that:

- **1,148,200** people in the United States are living with HIV
- **207,600** are unaware of their HIV status (~18.1%)
- **49,273** new HIV infections 2011—stable x 15 yrs
  - 2/3 in MSM
  - Blacks, urban poor, South
  - Prevalence is increasing

http://www.cdc.gov/hiv/topics/surveillance/basic.htm; Hall, JAMA 2008 300:520
Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2008–2011—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting.

* Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

* Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.
Diagnoses of HIV Infection among Adults and Adolescents, by Race/Ethnicity, 2008–2011—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.

*a Hispanics/Latinos can be of any race.
AIDS develops in 38% of HIV+ patients within 1 year of diagnosis

Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

- 2006: CDC advised testing for all persons aged 13 – 64 yrs
- Part of routine health care (opt-out)
- Test high risk annually, recent update suggests testing MSM every 3-6 mos
- ACP agrees

Seek, Test, Treat (Retain)

- Cost effective even if low prevalence (0.05 - 0.1%)
- Similar to screening for HTN, colon cancer, breast cancer
- Likely to extend survival, fewer OIs, decrease transmission

Routine Opt-Out Testing

- Has not been broadly implemented
- 45% of adults age 18-64 tested in US (2009 survey)
- CDC Provider Survey 2009 (20 states, 1718 providers)
  - 60% of all providers offered HIV screening to all patients ages 13-64
  - Most likely to offer testing
    - Nurse practitioners 5.6x more likely than physicians
    - Provider age < 50 2x more likely than ≥ 50
    - Black providers 2.6x more likely than white
    - Low/medium HIV patient loads 0.3x as likely

McNaghten, PLOS One 2013; 8:e51231
Outline

- HIV Epidemiology
- Treatment of HIV
- Preventing transmission
- Vaccines
- HIV cure research
Natural History of HIV

- Target: CCR5+ CD4 T cells+

HIV Life Cycle

Volberding, Lancet 2010 376:49
Antiretroviral Therapy (ART)

- Potent combination ART since 1996
- Major medical success of the late 20th century
  - Makes HIV a chronic manageable disease
- Effective ART can indefinitely suppress virus and restore immune function
- Improves quality of life
- Increases lifespan
- Decreases viral transmission
# Timeline of Antiretroviral Agents in US

<table>
<thead>
<tr>
<th>Year</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>Protease Inhibitor</th>
<th>Fusion/Entry Inh</th>
<th>Integrase Inh</th>
<th>Combination</th>
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<tbody>
<tr>
<td>1987</td>
<td>Zidovudine</td>
<td></td>
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<tr>
<td>1991</td>
<td>Didanosine*</td>
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<tr>
<td>1992</td>
<td>Zalcitabine*</td>
<td></td>
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</tr>
<tr>
<td>1994</td>
<td>Stavudine*</td>
<td></td>
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<td></td>
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<tr>
<td>1995</td>
<td>Lamivudine</td>
<td>Saquinavir*</td>
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<td></td>
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<tr>
<td>1996</td>
<td>Nevirapine</td>
<td>Ritonavir, Indinavir*</td>
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<tr>
<td>1997</td>
<td>Delavirdine*</td>
<td>Nelfinavir</td>
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<td>AZT+Lamivudine</td>
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<td>1998</td>
<td>Abacavir</td>
<td>Efavirenz</td>
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<tr>
<td>1999</td>
<td></td>
<td>Amprenavir*</td>
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<td></td>
<td></td>
<td>ABC+AZT+Lamivudine</td>
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<tr>
<td>2000</td>
<td></td>
<td>Lopinavir/RTV</td>
<td></td>
<td></td>
<td></td>
<td>ABC+AZT+Lamivudine</td>
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<tr>
<td>2001</td>
<td>Tenofovir</td>
<td></td>
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<td></td>
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<tr>
<td>2003</td>
<td>Emtricitabine (FTC)</td>
<td>Atazanavir, Fosamprenavir</td>
<td>Enfuvirtide (subc)</td>
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<tr>
<td>2004</td>
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<td></td>
<td></td>
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<td>ABC+Lam, TDF+FTC</td>
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<tr>
<td>2005</td>
<td>Tipranavir</td>
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<td>2006</td>
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<td>TDF+FTC+Efavirenz</td>
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<tr>
<td>2007</td>
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<td>Maraviroc</td>
<td>Raltegravir</td>
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<tr>
<td>2008</td>
<td>Etravirine</td>
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<tr>
<td>2011</td>
<td>Rilpivirine</td>
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<td></td>
<td></td>
<td>TDF+FTC+Rilpivirine</td>
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<tr>
<td>2012</td>
<td></td>
<td>Elvitegravir</td>
<td>TDF+FTC+Elv+Cobi</td>
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</tr>
</tbody>
</table>
Once Daily HIV Medications

- Very recently approved drugs have had great impact on multidrug-resistant virus and decreasing serious adverse effects
- Better adherence/success with once-daily combination tablets
HIV Medications Save Lives

1255 patients, at least one CD4 < 100/mm³

Figure 1. Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4⁺ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Non-AIDS Morbidity

- SMART study: 5472 pts who interrupted ART with CD4+ T cell count > 350, restart for CD4+ < 250 cells vs continuous therapy
- Interruption associated with higher mortality, predominantly due to non-HIV events: MI, cancer, ESRD, liver disease
- Growing as a proportion of cause of death

HIV associated with higher risk of non-AIDS events, reduced by ART

When to Start Medications

- Pendulum has swung back and forth about best time to initiate therapy
  - Numerous large cohort studies have shown survival benefit of starting earlier, easier to do now with less toxic and more convenient therapies
  - Effect of ART on prevention—public health benefit
- DHHS Panel guideline as of 2012: treat all persons with HIV
  - RCT data: CD4 < 350 cells/mm³
  - Observational, other trial data: CD4 < 500 cells/mm³
  - Expert opinion: CD4 > 500 cells/mm³

Life Expectancy at Age 20 (Europe, NA)

Cohort of >43,300 persons newly started on ART stratified by sex, CD4, IDU

Survival after starting cART (years)

<table>
<thead>
<tr>
<th>Year Interval</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-99</td>
<td>36 years</td>
</tr>
<tr>
<td>2000-02</td>
<td>41 years</td>
</tr>
<tr>
<td>2003-05</td>
<td>49 years</td>
</tr>
</tbody>
</table>

General population 64 yrs

Life expectancy ↓ for IDU, low baseline CD4+ count

ART Cohort Collab, Lancet 2008 372:293
HIV Natural History

- ART does not fully restore health
  - Patients remain at increased risk of complications associated with aging—CV disease, non-AIDS cancers, osteoporosis, renal disease, neurocognitive decline
- HIV and its treatment may be risks for accelerated aging/organ damage

Chronic Inflammation in HIV

- IL-6 and D-dimer levels have been associated with risk of serious events (e.g., CVD, non-AIDS cancers) or death in patients with HIV from large observational cohorts.
- Useful to follow to assess risk.

Grund, 20th CROI Washington, DC, March 2013, Abstr 60; Duprez, PLOS One 2012 7:e44454
Costs of HIV Medications

Wholesale price ~$20-25,000/person annually in US
- Modeling studies support cost effectiveness of ART
- 2011: $9 billion—mostly from government sources
- Waiting lists for ART in some states

- Generics widely used in low-income countries

- Some US generics available, more widely used drugs going off patent 2013 – 2017 (EFV 2013)
  - Could save $1 billion 1st yr; trade-off with taking multiple rather than single combination pills, ?lower potency

HIV in US

- Only 28% of HIV+ adults in the US have suppressed viral loads
- Undiagnosed HIV infection
- Failure to link and retain people with HIV into care

MMWR 2011 60:1618
Outline

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Pre-Exposure Prophylaxis for HIV

7/16/12: FDA approved the use of Truvada® for use in HIV negative persons to decrease risk of acquiring HIV

- RDBPCT of 2499 MSM 6 countries including US (iPrEx)
  - Median 1.2 yrs f/u
  - 44% reduction in HIV incidence with PrEP
  - 99% effective if therapeutic blood levels
  - Similar serious AEs

- 4 RDBPCT of Truvada® or TDF PrEP in heterosexuals (Africa)
  - 2 trials: 62 – 75% efficacy (high adherence)
  - 2 women’s trials stopped for futility—very low levels of adherence

Pre-Exposure Prophylaxis for HIV

- Very effective if taken consistently
- Should target high risk persons
- Physicians must:
  - Do initial and regular HIV/HBV/pregnancy testing
  - Counsel regularly on daily adherence
  - Provide comprehensive preventive services
  - Screen for and treat STIs
  - Monitor serum creatinine
- Other concerns: emergence of drug resistance, cost, side effects, pregnancy

Prevention of HIV with Early ART

- 1763 serodiscordant couples (97% heterosexual; Africa, India, Brazil, US, Thailand)
- Randomized to start ART with CD4+ 350-550 cells/mm3 vs defer until CD4+ < 250 cells/mm3

<table>
<thead>
<tr>
<th>Event</th>
<th>Event Rate/100 PY (95% CI)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmissions linked to HIV+ participant</td>
<td>Early ART: 0.1 (0.0 – 0.4)</td>
<td>Deferred ART: 1.7 (1.1 – 2.5)</td>
<td>0.04 (0.01 – 0.27)</td>
</tr>
</tbody>
</table>

- Decrease risk of HIV-related clinical event/death in early grp

Cohen NEJM 2011 365:493
Prevention of HIV

- Until recently, prevention trials have been disappointing with little consistent effect on HIV incidence

- How will increasingly scarce resources be used to curb the epidemic?

- Ideal is a protective vaccine
  - No dependence on adherence, chronic therapy, early detection

Padian, Lancet 2011 378:269
Outline

- HIV Epidemiology
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HIV Vaccine Obstacles

- Extensive viral subtype/sequence diversity
- Correlates of immune protection unknown
  - Likely will require antibody and T cell responses
- Viral escape (mutation, “hiding”, shielding of epitopes)
- Lack of a predictive animal models
- Costs
HIV Vaccines

> 220 vaccine trials, only 5 efficacy trials

Only one vaccine trial has demonstrated preventive effect in humans, (RV144)

Thailand, >16,000 M/F; canarypox vector vaccine boosted with recombinant gp120 vaccine led to 31% reduction in HIV incidence

Many more studies on vaccinees’ immune responses, booster studies, natural history of those infected

Safe

**HVTN 505 study began 2009, phase IIb, largest current trial**

- **N=2504, US MSM**
- DNA plasmid vaccine prime, boost with Ad5 vector expressing HIV antigens from 3 viral subtypes

**Interim analysis found that the vaccine did not prevent HIV or reduce VL in those infected**

- NS increase in HIV infections among vaccinees (3.3 vs 2.4%)

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Can HIV be cured?
Sterilizing vs Functional Cures

- **Sterilizing cure** = complete eradication of the virus from the body
- **Functional cure** = host control of HIV: undetectable virus in the blood in the absence of ART x yrs, immune function restored
  - Spontaneously occurs in “elite controllers”, ~1% of HIV-infected
  - Favorable HLA profile
  - Potent CD8+ T cell responses to HIV

Katlama, Lancet 2013 epub 3/28/13
HIV Latency

- Most CD4+ T cells that are infected with HIV produce virus and die
- Small subset of long-lived “resting” memory T cells persist indefinitely = latency
- Other cells may also harbor latent virus

HIV Reservoirs

- Despite potent ART, there remains a detectable pool of long-lived, latently infected CD4+ T cells with integrated, replication-competent virus
- Established within days of infection
- Latently infected cells do not express viral antigens on surface
- ART does not affect latent virus
- Interruption of ART leads to rapid viral rebound
- Likely that this pool is continuously being replenished by low level replication even in those on ART with undetectable viral loads

HIV Cure?

Timothy Brown, the “Berlin patient”
Berlin Patient Cure

CCR5 WT
HIV+
AML
ART d/c

Donor stem cells

Chemo TBI
GVHD

CCR5−
No plasma RNA/DNA, no culturable virus off ART x 5 yrs

More HIV Cures

- July 2012: 2 more HIV+ men in Boston underwent allogeneic SCT for lymphoma
  - Reported to be without evidence of HIV DNA or RNA in blood 2 – 3.5 yrs later
  - Remain on ART
  - Donors were not CCR5–
  - Both had GVHD

Henrich, XIX Int AIDS Conf, Washington DC, July 2012 Abstr THAA0101
Baby Functionally Cured

- Newborn at Univ Miss MC; mother HIV+, no prenatal care
  - HIV infection by DNA/RNA testing on day 2, persistently +VL to day 19 → AZT/3TC/NVP @ 31 hrs → AZT/3TC/LPV/r
  - Stopped ART at 18 mos, undetectable VL at 30 mos
  - 1 single plasma copy detected, could not culture virus from CD4+ T cells with sensitive assays
  - HIV antibody negative

- Was this a cure or an aborted infection?

Persaud, 20th CROI, Atlanta, GA March 2013 Abstr #48LB
Towards an HIV Cure

- Evidence of “cures”
- Unsustainability of providing lifelong drugs to 33 million people
  - Cost, adherence, delivery
  - Estimated that for every HIV-infected person who starts ART, 2 more are newly infected
- No imminent vaccine

Towards an HIV Cure

- Global Scientific Strategy Towards an HIV Cure announced at the International AIDS Conference July 2012

- Developed by IAS/world’s leading HIV/AIDS clinicians and basic science researchers
  - Develop strategy for cure rather than just better antiviral drugs and vaccines
  - Define main priorities in HIV cure research
    - Why does the virus persist in the presence of ART over decades?
    - In which tissues does the virus reside?
    - Why are elite controllers able to control the virus?
  - Advocacy for increased investment in HIV cure research

Current Clinical Cure Trials

- Activate virus from latency → RNA production → cell death, protection of bystander infection by ART ("Shock and Kill")
- Many compounds can reverse silencing of provirus in vitro

- Vorinistat (Zolinza® HDACi) single dose 8 pts with suppressed VL increased HIV RNA expression 4.8x from memory CD4+ T cells
- No effect on integrated DNA levels

Current Clinical Cure Trials

- Enhancing HIV specific immunity
  - Therapeutic vaccines
  - Blocking molecules that prevent T cell activation (PD-1)

- Making cells resistant to HIV
  - Make genetically modified T cells/stem cells resistant to HIV infection (e.g. CCR5 elimination via ex vivo use of zinc finger nucleases “gene scissors”)

Katlama, Lancet 2013 epub 3/28/13
Conclusions

- Ongoing need for HIV testing, treatment and prevention efforts given continued new HIV infections
- Encouraging trends in Africa’s epidemics but only ~50% of population in need receiving treatment
- Significant progress in treatment options
  - Easier and safer medications
  - Treatment as prevention
  - High costs
- No imminent vaccine options
- At least functional cures have been reported, intense research efforts in this area