HIV/HCV Screening in 2015: Where Are We Now?

Bernard M. Branson, M.D.
Disclosures

- Dr. Branson has no financial interests to disclose.
Terminology

- **Diagnostic testing:** performing a test based on clinical signs or symptoms
- **Targeted screening:** performing a test on subpopulations of persons at higher risk based on behavioral, clinical or demographic characteristics
- **Screening:** performing a test for all persons in a defined population
- **Opt-out screening:** performing a test after notifying the patient that the test will be done; consent is inferred unless the patient declines
For which patients would you order an HIV test?

0% A. Patients at high risk.
0% B. All adults and adolescent patients.
0% C. Only patients who request a test.
0% D. I don’t order HIV testing.
For which patients would you order an HCV test?

A. Patients at high risk.
B. All adults and adolescent patients.
C. Adults born between 1945 and 1965.
D. A and C
E. I don’t order HCV tests.

1. Enter answer text...
Criteria that Justify Routine Screening

1. Serious health disorder that can be detected before symptoms develop
2. Treatment is more beneficial when begun before symptoms develop
3. Reliable, inexpensive, acceptable screening test
4. Costs of screening are reasonable in relation to anticipated benefits
5. Treatment must be accessible

*Principles and Practice of Screening for Disease*
- WHO Public Health Paper, 1968
Screening: Cervical Cancer

Cervical CA

Annual new diagnoses: 12,109

Deaths: 4,092
## Screening: Cervical Cancer vs. HIV

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>Cervical CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual new diagnoses</td>
<td><strong>47,352</strong></td>
<td><strong>12,109</strong></td>
</tr>
<tr>
<td>Deaths</td>
<td><strong>17,173</strong></td>
<td><strong>4,092</strong></td>
</tr>
</tbody>
</table>
Screening works.
Estimated Number of Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985-2005 – United States

Number of cases

Year of diagnosis

PACTG 076 & USPHS ZDV Recs

CDC HIV Screening Recs

~95% reduction
Persons with HIV and Awareness of HIV Status, United States - 2012

Number HIV infected 1,201,100

Number unaware of their HIV infection 168,300 (14 %)

Estimated new infections annually 47,500

CDC HIV Surveillance Supplemental Report, 2014
Burden of HCV Infection and Disease

- United States
  - ~ 3.2 M (2.7-3.9) persons living with HCV
  - 29,700 new cases (2013)
  - 19,300 deaths

- CDC. Hepatitis Surveillance 2013
HIV and HCV Co-infection

- Prevalence of co-infection varies by region
  - 25% of HIV infected persons in US

- HIV hastens progression of HCV related liver disease

- Liver disease is second leading cause of death for persons with HIV

HCV in the Context of HIV in the US

HIV
1.2 million

HCV
3.2 million
How do annual deaths from HCV compare with annual deaths from HIV?

0%  A. Annual mortality is about the same.
0%  B. More people die from HIV.
0%  C. More people die from HCV.
Mortality associated With Hepatitis B, Hepatitis C, and HIV, United States, 1999 – 2008

Estimated Number of New HIV Infections by Transmission Category
50 U.S. States & DC, 1977-2006
HIV Prevalence and Incidence

The number of people living with HIV has grown because incidence is relatively stable and survival has increased.

![Graph showing HIV prevalence and incidence](image)

**New HIV Infections**  **Prevalence**

*Hall JAMA 2008; PreJean PloS One 2011; MMWR 2011*
Estimated Incidence of Acute Hepatitis C
United States, 1982 – 2012

- Discovery of HCV: 1989
- 1986 Indirect blood screening for non-A non-B (ALT)
- Anti-HCV test licensed: 1992

Incident cases per 100,000 persons

Year


HCV Prevalence by Year of Birth
The Future Burden of Hepatitis C in the United States

- Of 2.7 million HCV-infected persons in primary care
  - 1.47 million will develop decompensated cirrhosis (DCC)
  - 350,000 will develop hepatocellular carcinoma (HCC)
  - 897,000 will die from HCV-related complications

Rationale for Expanded Screening
Estimated Number of Adults and Adolescents Living with HIV Infection and Percent Undiagnosed – United States, 1985 - 2008

- No. living with undiagnosed HIV infection
- No. living with diagnosed HIV infection
- Percent undiagnosed

HAART

Year:
- 1985
- 1986
- 1987
- 1988
- 1989
- 1990
- 1991
- 1992
- 1993
- 1994
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011

Number:
- 0
- 20,000
- 40,000
- 60,000
- 80,000
- 100,000
- 120,000
- 140,000
- 160,000
- 180,000
- 200,000
- 220,000
- 240,000
- 260,000
- 280,000
- 300,000
- 320,000
- 340,000
- 360,000
- 380,000
- 400,000
- 420,000
- 440,000
- 460,000
- 480,000
- 500,000
- 520,000
- 540,000
- 560,000
- 580,000
- 600,000
- 620,000
- 640,000
- 660,000
- 680,000
- 700,000
- 720,000
- 740,000
- 760,000
- 780,000
- 800,000
- 820,000
- 840,000
- 860,000
- 880,000
- 900,000
- 920,000
- 940,000
- 960,000
- 980,000
- 1,000,000
- 1,020,000
- 1,040,000
- 1,060,000
- 1,080,000
- 1,100,000
- 1,120,000

Percent:
- 0.0
- 20.0
- 40.0
- 60.0
- 80.0
- 100.0
Positive HIV Tests, 1989-2012
CDC Funded Testing Sites

- CDC, HIV Counseling and Testing at CDC-Supported Sites, 1989 - 2012
<table>
<thead>
<tr>
<th>Year of HIV Dx</th>
<th>Number of Dx</th>
<th>AIDS in 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>18,016</td>
<td>43.2</td>
</tr>
<tr>
<td>1997</td>
<td>16,882</td>
<td>41.5</td>
</tr>
<tr>
<td>1998</td>
<td>15,429</td>
<td>41.6</td>
</tr>
<tr>
<td>1999</td>
<td>23,295</td>
<td>40.6</td>
</tr>
<tr>
<td>2000</td>
<td>28,842</td>
<td>39.5</td>
</tr>
<tr>
<td>2001</td>
<td>38,818</td>
<td>36.4</td>
</tr>
<tr>
<td>2002</td>
<td>36,244</td>
<td>36.7</td>
</tr>
<tr>
<td>2003</td>
<td>33,826</td>
<td>37.7</td>
</tr>
<tr>
<td>2004</td>
<td>35,645</td>
<td>37.6</td>
</tr>
<tr>
<td>2005</td>
<td>34,424</td>
<td>36.4</td>
</tr>
<tr>
<td><strong>2009</strong></td>
<td><strong>46,454</strong></td>
<td><strong>32.7</strong></td>
</tr>
<tr>
<td><strong>2012</strong></td>
<td><strong>41,711</strong></td>
<td><strong>24.0</strong>*</td>
</tr>
</tbody>
</table>

A total of 76,122 HCV diagnoses were reported to the MDPH between 1992 and 2009, 8,499 of these reported HCV cases died and are represented in the figure.
Why Screen in Healthcare Settings?

*(because that’s where the money is)*
Source of HIV Tests and Positive Tests

- 60% of adults age 18-64 have been tested
- 18 million adults age 18-64 tested annually in U.S.

<table>
<thead>
<tr>
<th>Source</th>
<th>HIV tests*</th>
<th>HIV diagnoses**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private doctor/HMO</td>
<td>53%</td>
<td>18%</td>
</tr>
<tr>
<td>Hospital, ED, Outpatient</td>
<td>18%</td>
<td>32%</td>
</tr>
<tr>
<td>Community clinic (public)</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>HIV counseling/testing</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Correctional facility</td>
<td>0.4%</td>
<td>4%</td>
</tr>
<tr>
<td>STD clinic</td>
<td>0.1%</td>
<td>5%</td>
</tr>
<tr>
<td>Drug treatment clinic</td>
<td>0.4%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*National Health Interview Survey, 2006  
**HIV Surveillance System, 2007
Emergency Departments
Rapid HIV Testing in the ED

- Rapid HIV testing 2003
  - 62% accept HIV testing
  - 98% receive test results
  - 3,305 patients screened
  - 83 (2.5%) new HIV positive
  - 80% entered HIV care (median 18 days)

- HIV tests ordered by ED providers increased from 5 to 29 per month

- Lyss et al, JAIDS 2007
## Characteristics, HIV-Positive Patients Identified in ED Screening

<table>
<thead>
<tr>
<th>No previous test</th>
<th>47 (57%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>30 (34%)</td>
</tr>
<tr>
<td>IDU</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>High risk hetero partner</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

- Lyss et al, JAIDS 2007
Characteristics, HIV-Positive Patients Identified in ED Screening

N= 83

No previous test 47 (57%)

Risk factors

  MSM 30 (34%)
  IDU 8 (10%)
  High risk hetero partner 3 (4%)
  No identified risk 42 (51%)

- Lyss et al, JAIDS 2007
Missed Opportunities: South Carolina

- All reported cases of HIV, 2001 - 2005

- Confidentially matched with registry of health care visits

*MMWR 55:47, December 1, 2006*
Missed Opportunities: South Carolina

- 4,315 reported HIV cases
  - 3,157 (73%) made 20,271 health-care visits prior to their first positive HIV test
  - Diagnosis codes at 15,648 (77%) of prior visits would not have prompted an HIV test

MMWR 55:47, December 1, 2006
Missed Opportunities: South Carolina

- 1,784 (42%) developed AIDS within 1 year

- 1,302 (73%) made 7,988 previous health-care visits (median 4 per patient) but were not tested for HIV

- Diagnosis codes for 6,277 (79%) of prior visits would not have prompted an HIV test

MMWR 55:47, December 1, 2006
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings
CDC Expanded HIV Testing Initiative

Percent of Total Tests and New HIV+ Tests by Venue, Oct 2007 - Sept 2010

- **Total Tests**
  - **Inpatient**: 1.5
  - **Urgent Care**: 0.4
  - **STD Clinics**: 21
  - **Corrections**: 15
  - **Subst Abuse**: 1
  - **TB Clinics**: 17
  - **CHCs**: 12
  - **Other**: 8

- **HIV+ Tests**
  - **Inpatient**: 1
  - **Urgent Care**: 0.5
  - **STD Clinics**: 20
  - **Corrections**: 14
  - **Subst Abuse**: 0.9
  - **TB Clinics**: 0.7
  - **CHCs**: 8
  - **Other**: 8.2

**Percent of Venues**
- **8%**

**Percent of Tests**
- **30**
- **32**
- **21**
- **15**
- **14**
- **17**
- **12**
- **8**
- **8.2**
Risk-based HCV Testing Strategies

- Prior CDC recommendations:
  - Injection drug use
  - Blood transfusion before 1992 and other blood exposures

- Many clinicians are not aware of HCV testing guidelines or patients’ risks.

- 45-60% of persons with HCV remain unaware of their HCV infection
Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965
2013 HIV Recommendation statement

- Adolescents and adults ages 15 to 65 years – Grade A
- All pregnant women – Grade A
2013 HCV Recommendation statement

- Persons at high risk for infection – Grade B
- Adults born between 1945 and 1965 – Grade B
Why USPSTF Grades Matter

Health Care Reform:

SEC. 2713. COVERAGE OF PREVENTIVE HEALTH SERVICES.

(a) IN GENERAL.—A group health plan and a health insurance issuer offering group or individual health insurance coverage shall, at a minimum, provide coverage for and shall not impose any cost sharing requirements for—

(1) evidence-based items or services that have in effect a rating of ‘A’ or ‘B’ in the current recommendations of the United States Preventive Services Task Force;
1. The Medical Rationale

- Treatment for HIV is Effective.

- Treatment is recommended for all patients with HIV, regardless of CD4 count
  - March 2012 – DHHS Treatment Guidelines

- Treatment can cure HCV
HIV Antiretroviral Therapy Improves Survival

Mortality and HAART Use Over Time
HIV Outpatient Study, CDC, 1994-2003
HCV Therapy Can Eliminate HCV Infection and Reduce Morbidity/Mortality Risks

- Therapy can cure HCV infection - sustained virologic response (SVR)

- SVR is associated with
  - 70% reduction in Hepatocellular carcinoma
  - 50% reduction in all-cause mortality

Which of the following is true about therapy for HCV?

0%  A. Treatment requires a minimum of 6 months.
0%  B. Treatment always includes interferon.
0%  C. Treatment is effective for ~2/3 of patients.
0%  D. All of the above.
0%  E. None of the above.
Advances in HCV Therapy

Sustained Virologic Response (%)


IFN 6 m  6%  16%  34%  42%  39%  >90%
IFN 12 m  ??  ??  ??  ??  ??  ??
IFN/RBV 6 m  ??  ??  ??  ??  ??  ??
IFN/RBV 12 m  ??  ??  ??  ??  ??  ??
Peg-IFN (PEG) 12 m  ??  ??  ??  ??  ??  ??
Peg/IFN 12 m  ??  ??  ??  ??  ??  ??
Peg/RBV 6 m  54 – 56%  67-72%  ??  ??  ??  ??
Peg/RBV 12 m  ??  ??  ??  ??  ??  ??
All oral DAA 12 wk  ??  ??  ??  ??  ??  ??

Adapted from Strader DB, et al. Hepatology. 2004
## Interferon-Free HCV Regimens Approved

<table>
<thead>
<tr>
<th>PROTEASE</th>
<th>POLYMERASE</th>
<th>NS5A INHIBITOR</th>
<th>OTHER</th>
<th>APPROVAL DATE</th>
<th>GENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sofosbuvir</td>
<td>Ribavirin</td>
<td>December 2013</td>
<td>2, 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>October 2014</td>
<td>1, 4</td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td></td>
<td>November 2014</td>
<td>1, 4</td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/ritonavir</td>
<td>Dasabuvir</td>
<td>Ombitasvir</td>
<td>Ribavirin</td>
<td>December 2014</td>
<td>1, 4</td>
</tr>
</tbody>
</table>
ION-1: SOF/LDV in Naïve HCV, GT1

Afdhal, NEJM 2014
ION-4: SOF/LDV in HIV/HCV

Naggie, CROI 2015; Abs LB 152

SVR12

Overall 321/335
Naïve 142/150
Experienced 179/185
No Cirrhosis 258/268
Cirrhosis 63/67
2. The Business Case

How Much Does It Cost?

It Depends.

<table>
<thead>
<tr>
<th></th>
<th>Submitted Charges</th>
<th>Plan Allowance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Antibody</td>
<td>$127</td>
<td>$11.02</td>
</tr>
<tr>
<td>HCV Antibody</td>
<td>$150</td>
<td>$19.42</td>
</tr>
</tbody>
</table>
# HIV: Costs Go Up as CD4 Counts Go Down

<table>
<thead>
<tr>
<th>CD4 Category</th>
<th>Total Cost</th>
<th>ARV Meds</th>
<th>Other Meds</th>
<th>Hospital</th>
<th>Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;350</td>
<td>$13,855</td>
<td>$9407</td>
<td>$1855</td>
<td>$1408</td>
<td>$285</td>
</tr>
<tr>
<td>200-349</td>
<td>$18,274</td>
<td>$11,935</td>
<td>$3452</td>
<td>$1186</td>
<td>$336</td>
</tr>
<tr>
<td>50-199</td>
<td>$23,864</td>
<td>$11,862</td>
<td>$6685</td>
<td>$3369</td>
<td>$532</td>
</tr>
<tr>
<td>&lt;50</td>
<td>$36,532</td>
<td>$10,855</td>
<td>$14,882</td>
<td>$8,353</td>
<td>$533</td>
</tr>
</tbody>
</table>

635 Patients, Univ Alabama Birmingham  
- Chen et al, Clin Inf Disease 2006
## Early HIV Diagnosis: Substantial Benefit with Little Extra Cost

<table>
<thead>
<tr>
<th>Initial CD4 Count</th>
<th>Life Expectancy</th>
<th>Lifetime Medical Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;199</td>
<td>8.5</td>
<td>$192,325</td>
</tr>
<tr>
<td>200-499</td>
<td>15.4</td>
<td>$195,318</td>
</tr>
<tr>
<td>&gt;500</td>
<td>24.4 years</td>
<td>$230,044</td>
</tr>
</tbody>
</table>

- Hutchinson et al, JAIDS 2006
3. Potential Effects on Transmission
Persons Whose HIV is Diagnosed Are Less Likely to Transmit

After people become aware they are HIV-positive, the prevalence of high-risk sexual behavior is reduced substantially.

Reduction in Unprotected Anal or Vaginal Intercourse with HIV-neg partners:
HIV-pos Aware vs. HIV-pos Unaware

68%

Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the U.S.
ART Stops HIV Transmission

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H.,
Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D.,
Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D.,
Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D.,
Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D.,
Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A.,
Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D.,
Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch.,
Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D.,
Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D.,
Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S.,
Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M.,
and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*
HPTN 052: HIV Transmissions

1,763 sero-discordant couples (97% heterosexual)
HIV infected partners: 890 men, 873 women

39 HIV transmissions

28 linked HIV transmissions
11 unlinked transmissions

Immediate ART: 1 transmission
Deferred ART: 27 transmissions

96% reduction with ART

- Cohen M et al, NEJM 2011
HIV and HCV Transmission Among People Who Inject Drugs

- Transmission risks
  - Injection duration
  - Frequency of injecting
  - Equipment sharing, not just sharing needles

- Incidence declined in response to harm reduction for HIV (e.g., syringe access programs)
Antiviral Therapy Might Be Used to Reduce HCV Prevalence among Injecting Drug Users

- Can the HIV model of “Treatment as Prevention" be applied to HCV?
- Annually treating 10 HCV infections per 1000 IDU and achieve SVR of 62.5%
- Projected to result in a relative decrease in HCV prevalence over 10 years of 31%, 13%, or 7% for baseline prevalences of 20%, 40%, or 60%, respectively

Martin et al. Journal of Hepatology 2011 vol. 54 j 1137–1144
HIV, HBV, alcohol, and steatosis can accelerate disease progression

Acute HIV: Clinical Syndrome

- 40-90% develop symptoms of Acute HIV
- 50%-90% with symptoms seek medical care
- Of those diagnosed with Acute HIV, 50% of patients seen at least 3 times before diagnosis

- Kahn et al, NEJM 1998
- Weintrob et al, Arch Int Med 2003
Clinical Manifestations

101 seroconverters, HIVNET cohort 1995-98

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent</th>
<th>Median Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptom</td>
<td>85%</td>
<td>Days (IQR)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56%</td>
<td>9 (5-29)</td>
</tr>
<tr>
<td>Fever</td>
<td>55%</td>
<td>5 (4-10)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>43%</td>
<td>7 (5-10)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>36%</td>
<td>7 (4-14)</td>
</tr>
<tr>
<td>Rash</td>
<td>16%</td>
<td>8 (6-14)</td>
</tr>
</tbody>
</table>

- Celum et al, JID 2001
Frequency of Acute HIV among Patients Seeking Care

- 1.2% among 563 patients evaluated for infectious mononucleosis\(^1\)

- 1.2% among 499 patients evaluated in urgent care for acute viral illness\(^2\)

\(^1\)Rosenberg et al, N Engl Journal 1999
\(^2\)Pincus et al, Clin Infectious Disease 2003
Phoenix ED Screening July 2011 through February 2013

- 4th gen screening of patients who had blood drawn
  - 15% of patients declined testing
  - 13,014 patients tested
  - 37 (0.3%) new HIV infections
    - 12 (32.4%) had Acute HIV Infection (antibody negative)

- Median viral load:
  - Patients with acute infections: 3.6 million
  - Patients with established infections: 27,000

-MMWR June 21, 2013
Acute Infections in MSM detected by RNA only

- 0.3% of 14,005 frequently tested MSM in Seattle STD clinic; **20% of all HIV infections detected**
  - Stekler et al, Clin Infect Dis 2009

- 26 (74%) of 35 AHI cases detected in LA at MSM clinic; **25% of all HIV infections detected**
  - Patel et al, Archives Int Med 2010

- 0.08% of 21,425 STD clinic patients in New York City; **9% of all HIV infections detected**
  - 94% were MSM
  - Shepard et al, MMWR 2009
Why Is Acute HIV Important?
Increased Risk of Sexual Transmission of HIV

Virus 75 times more infectious

Acute HIV: Partner Notification

- Persons with acute HIV infection
  - 2.5 times as many sex partners
  - 1.9 times as many partners newly diagnosed with HIV

...as did persons with new diagnosis of established HIV infection

Moore et al, JAIDS 2009
HIV-1 Transmission, by Stage of Infection and Behavior Pattern

<table>
<thead>
<tr>
<th>Infection Stage</th>
<th>Transmission Hazard per Person-year</th>
<th>Mean Duration, Years (%)</th>
<th>No. (%) New Transmissions, by Sexual Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>2.76</td>
<td>0.24 (2%)</td>
<td>Serial Monogamy: 0.10 (9%) Random Mixing: 0.67 (31%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.106</td>
<td>8.38 (82%)</td>
<td>Serial Monogamy: 0.77 (71%) Random Mixing: 0.91 (42%)</td>
</tr>
<tr>
<td>AIDS</td>
<td>0.760</td>
<td>0.75 (16%)</td>
<td>Serial Monogamy: 0.21 (20%) Random Mixing: 0.57 (27%)</td>
</tr>
</tbody>
</table>

Hollingsworth et al, JID 2008
What tests to use?
Evolution of HIV Tests: Four Generations
Evolution of HIV Tests

- 1\textsuperscript{st} generation: whole viral lysate, detects IgG antibody
EIA

Western blot

IFA

1st Generation
Evolution of HIV Tests

- **1st generation**: whole viral lysate, detects IgG antibody

- **2nd generation**: synthetic peptides, detects IgG antibody
OraQuick Advance

Multispot HIV-1/HIV-2

Clearview Complete

MedMira Reveal G3

INSTI

Chembio Stat Pak

2nd Generation
Evolution of HIV Tests

- 1\textsuperscript{st} generation: whole viral lysate, detects IgG antibody
- 2\textsuperscript{nd} generation: synthetic peptides, detects IgG antibody
- 3\textsuperscript{rd} generation: detect IgM and IgG antibody
Bio-Rad GS HIV-1/2 PLUS O
2003

Unigold Recombigen
2003

Siemens Advia Centaur
2006

Ortho Vitros
2008

3rd Generation
Random Access Multiplatform analyzers for HIV testing

On-board Refrigeration of Multiple Different Assays
Random Access Multiplatform analyzers for HIV testing

STAT sample requests without pausing
Results in <60 minutes
Evolution of HIV Tests

- 1\textsuperscript{st} generation: whole viral lysate, detects IgG antibody
- 2\textsuperscript{nd} generation: synthetic peptides, detects IgG antibody
- 3\textsuperscript{rd} generation: detects IgM and IgG antibody
- 4\textsuperscript{th} generation: detects IgM, IgG antibodies, p24 antigen
Abbott Architect Ag/Ab Combo
2010

Control    Antigen    Antibody

Bio-Rad Ag/Ab Combo
2011

Determine Combo Ag/Ab Rapid Test
2013

4th Generation
HIV Infection and Laboratory Markers

26 seroconverters were analyzed with 14 tests
17 seroconverters with WB positive used for cumulative frequency analysis
Sequence of Test Positivity Relative to WB (plasma)

166 specimens, 17 Seroconverters - 50% Positive Cumulative Frequency


Luo et al, J Clin Virol 2013
RNA vs. 4th Generation Ag/Ab Assay

RNA+/ 3rd gen-negative specimens detected by 4th generation EIA:

- 38 of 46 (83%) – Australia*
- 10 of 14 (71%) – CDC AHI study**
- 51 of 61 (84%) – CDC panel***

- 4 days after RNA – 9 seroconversion panels***

* Cunningham P, HIV Diagnostics Conf 2007
** Patel P, CROI 2009
*** Owen M, CROI 2009
3rd & 4th gen lab screening tests

1987 Vironostika EIA
1992 Abbott HIV-1/HIV-2 EIA
2000 Genetic Systems HIV-1/HIV-2 Peptide EIA
2003 GS HIV-1 HIV-2 Plus O EIA
2006 Advia Centaur 1/O/2 CIA
2008 Ortho Vitros HIV 1+2 CIA
2010 Abbott Architect Ag/Ab Combo CIA
2011 Bio-Rad Ag/Ab Combo EIA

1st gen confirmatory tests

1985 Abbott HIV-1 EIA
1992 Fluorognost IFA
1998 Genetic Systems rLAV (HIV-1)
1991 Cambridge Western blot

2nd gen rapid tests

2002 OraQuick HIV-1/HIV-2 Rapid Test
2004 Multispot HIV-1/HIV-2 Rapid Test
2003 Unigold Reveal HIV-1 Rapid Tests
2006 Aptima Qualitative RNA
2009 Avioq HIV-1 EIA
2010 INSTI HIV-1 Rapid Test
2013 Determine Combo Ag/Ab Rapid test
Why Does It Matter?

- Sensitivity among frequently-tested MSM in Seattle

- 192 infected with HIV
  - 23 (12%) detected only by RNA
    - (15/16 tested detected by Ag/Ab immunoassay)
  - 169 (88%) detected by serum Ab immunoassay
  - 153 (80%) detected by oral fluid rapid test

- Stekler et al, Clin Inf Dis 2009
The Public Health Service recommends that no positive test results be given to clients/patients until a screening test has been repeatedly reactive on the same specimen and a supplemental, more specific test such as the Western blot has been used to validate those results.
Limitations of 1989 HIV-1 Algorithm

- Antibody tests do not detect infection in ~ 10% of infected persons at highest risk of transmission.

- Western blot confirmation is less sensitive during early infection than many widely used screening tests.

- Antigen/antibody combo tests now FDA-approved that can detect most antibody-negative persons during highly infectious acute infection stage.
HIV-2 Infection

- **Remains uncommon in U.S., but**
  - Does not respond to NNRTIs, some PIs (first line therapy)
  - Undetectable by HIV-1 viral load tests

- **Misclassification by HIV-1 Western blot:**
  - 54/58 (93%) HIV-2 patients tested had positive HIV-1 WB (NYC)*
  - 97/163 (60%) HIV-2 cases reported had positive HIV-1 WB (CDC)**

- **HIV-2 often diagnosed after immunologic deterioration in patient with negative viral load**

*Torian et al, Clinical Infectious Disease 2010
**MMWR July 2011
Laboratory Testing for the Diagnosis of HIV Infection

Updated Recommendations

Published June 27, 2014

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4th generation HIV-1/2 immunoassay

(+)

(-)

Negative for HIV-1 and HIV-2 antibodies and p24 Ag

HIV-1/HIV-2 antibody differentiation immunoassay

HIV-1 (+) HIV-1 (-) HIV-1 (+) HIV-1 (-) or indeterminate
HIV-2 (-) HIV-2 (+) HIV-2 (+) HIV-2 (-)

HIV-1 antibodies detected HIV-2 antibodies detected HIV antibodies detected

NAT

NAT (+) NAT (-)

Acute HIV-1 infection Negative for HIV-1
FDA-approved HIV-1/HIV-2 Antibody Differentiation Assay

Reactive Control

Recombinant HIV-1

Peptide HIV-2

Peptide HIV-1
Geenius HIV-1/2 Supplemental Assay

FDA-approved October 2014
The Geenius™ HIV-1/2 Lines

HIV-1 & HIV-2 Associated Lines

Control Band

gp36

HIV-2

gp140

HIV-1

gp41 (group M & O)

p31*

p24

gp160

* inside the nucleocapsid
The Geenius Software

- Automated reading and validated results generation
- Pre-programmed and validated assay validity criteria
- Archiving of test results including a picture of each cassette
- Interface with LIS
<table>
<thead>
<tr>
<th>HIV-1 RESULT</th>
<th>HIV-2 RESULT</th>
<th>ASSAY INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>HIV NEGATIVE</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Negative</td>
<td>HIV-1 INDETERMINATE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Negative</td>
<td>Indeterminate</td>
<td>HIV-2 INDETERMINATE&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Indeterminate</td>
<td>HIV INDETERMINATE&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>HIV-1 POSITIVE</td>
</tr>
<tr>
<td>Positive</td>
<td>Indeterminate</td>
<td>HIV-1 POSITIVE</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>HIV-2 POSITIVE</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Positive</td>
<td>HIV-2 POSITIVE</td>
</tr>
</tbody>
</table>

**HIV-2 POSITIVE with HIV-1 cross-reactivity:** Antibody to HIV-2 confirmed in the sample. HIV-1 positivity (with only one HIV-1 envelope band, gp160 or gp41), is due to cross-reactivity and precludes confirmation of HIV-1<sup>*</sup>.  
<sup>*</sup>Note: Differentiation features managed by proprietary algorithm.

**HIV POSITIVE Untypable (undifferentiated):** Antibodies to HIV-1 and HIV-2 confirmed in the sample. This may occur in an HIV-2 positive sample with significant cross-reactivity to HIV-1, or may be due to co-infection with both HIV-1 and HIV-2 (rare)<sup>*</sup>.  
<sup>*</sup>Note: Differentiation features managed by proprietary algorithm.

<sup>a</sup> HIV-1 band(s) detected but did not meet the criteria for HIV-1 Positive  
<sup>b</sup> HIV-2 band(s) detected but did not meet the criteria for HIV-2 Positive  
<sup>c</sup> HIV band(s) detected but did not meet the criteria for HIV-1 Positive or HIV-2 Positive
Implications

Ability to detect acute HIV infection
- Focus for partner services and intervention efforts
- New surveillance case definition: **Stage 0**

Ability to detect HIV-2 infections
- False-Negative results with viral load tests
- Do not respond to many ARVs, e.g. NNRTI’s and several protease inhibitors
On the Horizon…
“Point-of-Care” Nucleic Acid Tests

- Alere q HIV-1/2 Detect
- GeneXpert
- SAMBA II
Testing for HCV Infection: An Update of Guidance for Clinicians and Laboratorians
Laboratory testing to identify HCV infection

HCV ANTIBODY

NON-REACTIVE

No HCV infection

REACTIVE

HCV RNA

POSITIVE

Current HCV Infection

NEGATIVE

No current HCV Infection

Additional testing as appropriate

Current HCV Infection

Additional testing as appropriate

No HCV infection

No HCV infection
Persons at highest risk for severe complications are a priority for HCV treatment

- Advanced fibrosis
- Compensated cirrhosis
  - HCV treatment is most likely to provide the most immediate and significant benefits
  - Burden of these is unknown in the US population

IDSA/AASLD  http://hcvguidelines.org/
**CDC Study with Quest Diagnostics**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of HCV-related tests available in the dataset</td>
<td>9,785,956</td>
</tr>
<tr>
<td>Number of tests with valid ID</td>
<td>7,255,188</td>
</tr>
<tr>
<td>Number of HCV RNA positive tests</td>
<td>465,814</td>
</tr>
<tr>
<td>Unique HCV RNA positive persons</td>
<td>273,207</td>
</tr>
<tr>
<td>Persons with FIB-4 ±30 days</td>
<td>125,290</td>
</tr>
<tr>
<td>• Born 1945-1965 (screening cohort)</td>
<td>86,741 (68.2%)</td>
</tr>
</tbody>
</table>

-*Klevens, CROI 2015*
**FIB-4 is a strong correlate of biopsy results**

<table>
<thead>
<tr>
<th>DEGREE OF FIBROSIS (STAGE)</th>
<th>IASL</th>
<th>Metavir</th>
<th>Mean APRI score (95% CIs)</th>
<th>Mean FIB-4 score (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis (N= 242)</td>
<td>No fibrosis (0)</td>
<td>F0</td>
<td>0.39 (0.36-0.43)</td>
<td>1.04 (0.96-1.13)</td>
</tr>
<tr>
<td>Fibrous portal expansion (N= 483)</td>
<td>Mild-portal Fibrosis (1)</td>
<td>F1</td>
<td>0.49 (0.46-0.52)</td>
<td>1.31 (1.23-1.38)</td>
</tr>
<tr>
<td>Few bridges or septa (N=616)</td>
<td>Moderate fibrosis (2)</td>
<td>F2</td>
<td>0.69 (0.64-0.73)</td>
<td>1.56 (1.48-1.64)</td>
</tr>
<tr>
<td>Numerous bridges or septa (N=388)</td>
<td>Severe fibrosis (3)</td>
<td>F3</td>
<td>1.08 (0.99-1.17)</td>
<td>2.40 (2.25-2.57)</td>
</tr>
<tr>
<td>Cirrhosis (N= 452)</td>
<td>Cirrhosis (4)</td>
<td>F4</td>
<td>1.51 (1.39-1.64)</td>
<td>3.79 (3.54-4.05)</td>
</tr>
</tbody>
</table>

Holmberg S et al. CID 2013; 57(2): 240-6
Calculation of FIB-4

\[
\text{FIB} - 4 - \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count (10}^9/\text{L}) \times [\text{ALT (U/L)}]^{1/2}}
\]
### Percentage of Persons with a Positive HCV-RNA by Birth Cohort and FIB-4 Measure

<table>
<thead>
<tr>
<th></th>
<th>&lt;1945</th>
<th>1945-1965</th>
<th>&gt;1965</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.2</td>
<td>9.0</td>
<td>55.3</td>
<td>19.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>20.1</td>
<td>39.2</td>
<td>28.5</td>
<td>35.3</td>
</tr>
<tr>
<td>Severe</td>
<td>37.9</td>
<td>26.2</td>
<td>6.7</td>
<td>22.4</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>35.9</td>
<td>21.1</td>
<td>4.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Missing/Unknown</td>
<td>5.0</td>
<td>4.5</td>
<td>5.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Total N</td>
<td>8,521</td>
<td>86,741</td>
<td>29,814</td>
<td>125,076</td>
</tr>
</tbody>
</table>
Persons in Need of Treatment

- About one-half of HCV-infected persons born from 1945-1965 had severe fibrosis or cirrhosis as measured by FIB-4 scoring.
- Of all persons with severe fibrosis or cirrhosis, 81% were born from 1945-1965.
- Need is urgent to:
  - identify HCV-infected persons
  - link them to management and care

-Klevens, CROI 2015
Effective treatment is available for both HIV and HCV.

HIV screening is recommended annually for persons at high risk and at least once in health care settings for all adults ages 15-64.

HCV screening is recommended for persons at high risk and one time for all persons born between 1945-65.

Early diagnosis benefits both treatment and prevention.