HIV/AIDS & Hepatitis C: Contrasting Pathways in Prevention and Treatment

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Some interesting contrasts between hepatitis C and HIV

HEPATITIS C

- 1. Always reportable by name in California
- 2. Written consent was never needed for testing
- 3. About 3-4 million infected in US
- 4. Hardly any money for prevention and treatment

HIV

- 1. Not reportable by name until 2006
- 2. Written consent was formerly needed for testing
- 3. About 1.1 million infected in US
- 4. Lots of money for prevention and treatment

More interesting contrasts between hepatitis C and HIV, the "Continuum of Care"

HEPATITIS C (U.S.)

- 1. 50% tested
- 2. 38% in care
- 3. 18% treated
- 4. 14% sustained virological response

(estimates based on survey)

HIV (U.S.)

- 1. 80%
- 2. 62%
- 3. 36% treated
- 4. 28% undetectable viral load

(based on studies of CDC data, 2011)

How could discrepancies be addressed for better prevention and treatment?

- If HIV/AIDS could be treated in a less exceptional manner, techniques that have been successful in controlling syphilis and TB could be more easily applied (e.g., reporting, partner notification, routine screening, and case management to influence safe behavior)
- If hepatitis C could achieve attention and funding on the scope of HIV/AIDS, control and treatment efforts could be more proportional to the magnitude of the problem

Interactions between HIV and hepatitis C

- Many drug users with HIV also acquired hepatitis C through the same means (needle sharing).
- Since hepatitis C is much more prevalent, a high proportion of HIV patients also have hepatitis C, but the proportion of hepatitis C patients with HIV is relatively small.
- HIV promotes hepatitis C progression to cirrhosis, cancer, and liver failure, so that severe liver disease occurs earlier.

Interactions between HIV and hepatitis C, contd.

- Hepatitis C also makes it harder to treat HIV
  - Many drugs must be metabolized by the liver.
  - Drugs for HIV may further damage the liver.
- Hepatitis C increases mortality by 50% in patients with AIDS http://www.aidsmap.com/Co-infection-with-hepatitis-C-increases-mortality-risk-by-50-for-patients-with-AIDS/page/2338061/
- Annual U.S. deaths from hepatitis C now exceed those from HIV/AIDS http://www.aidsmeds.com/articles/hiv_hcv_deaths_1667_21929.shtml
- Treatment recommendations for hepatitis C not changed by presence of HIV, but more effective in HIV-negative.

Interactions between HIV and hepatitis C, contd.

- HIV patients also infected with hepatitis C are not as able to suppress hepatitis C, and have larger numbers of hepatitis C viruses in their plasma and livers.
- Hepatitis C may be more infectious sexually and from mother to infant in HIV co-infected patients.

Comparing the viruses: HIV and HCV

- Both HIV and HCV are RNA viruses
  - do most of their damage through insidious, chronic infection after long asymptomatic periods.
- Both HIV and HCV mutate frequently
  - causing enough variability in surface proteins to evade antibody attacks
  - antibodies are a marker for infection rather than evidence of immunity.
- For hepatitis C, most transmission is by needle and only minimally by sex
- For HIV, most transmission is by sex and secondarily by needle.

Comparing the HIV and hepatitis C epidemics in the U.S.

- Incidence of hepatitis C in the U.S. is past its peak, but the impact of eventual cirrhosis, liver failure, and liver cancer from already-infected persons will be immense.
- HIV incidence has been stable, but prevalence is increasing, in part because of longer life spans
- Supposing hepatitis C were only 20% as deadly as HIV but the prevalence is 5 times higher, how will the ultimate mortality compare?
  - Actual mortality will depend on effectiveness of future treatments as well as on courses of the epidemics

HIV at its Worst: HIV prevalence in 5 countries in sub-Saharan Africa before treatment introduction (lower now) *Source: UNAIDS 2000 Update*

	South Africa	Botswana	Namibia	Lesotho	Swaziland
Population (000s)	39,900	1,597	1,695	2,108	980
Population 5-49 (000s)	20,982	786	795	1,000	468
% of Total Popn. w/HIV	10.50%	18.20%	9.40%	11.40%	13.30%
HIV Infected People (000s)	4,200	290	160	240	130
Adult Prev. Rate of HIV	20.00%	35.80%	19.50%	23.60%	25.30%
% of HIV in Females	54.80%	51.20%	53.10%	54.20%	51.50%
Pregnant Women HIV Prev.	19.20%	43.00%	25.90%	N/A	30.30%
AIDS Orphans (Living	370,952	54,943	53,023	29,469	10,705

OK, that's Africa; how about the U.S. - Is HIV under control here?

- Estimated 45-50,000 new cases continue to occur yearly
  - Actually represents overlap of epidemic course in multiple sub-population groups
    - Increasing in young gay males
    - Decreasing in black females and ? injection drug users
- Recent resurgence of syphilis among and accompanied by HIV infections among young gay males.

Other ominous HIV trends in U.S.

- Published reports show infected men who are told their HIV viral loads are low or undetectable sometimes assume they are not infectious, and reduce safe behavior.
- Increases in "barebacking" and "bug-chasing" (intentionally becoming infected) have been reported.
- 50% of new HIV cases are occurring in African-Americans.

Prevalence of HCV (Hepatitis C Virus) Antibody in U.S.

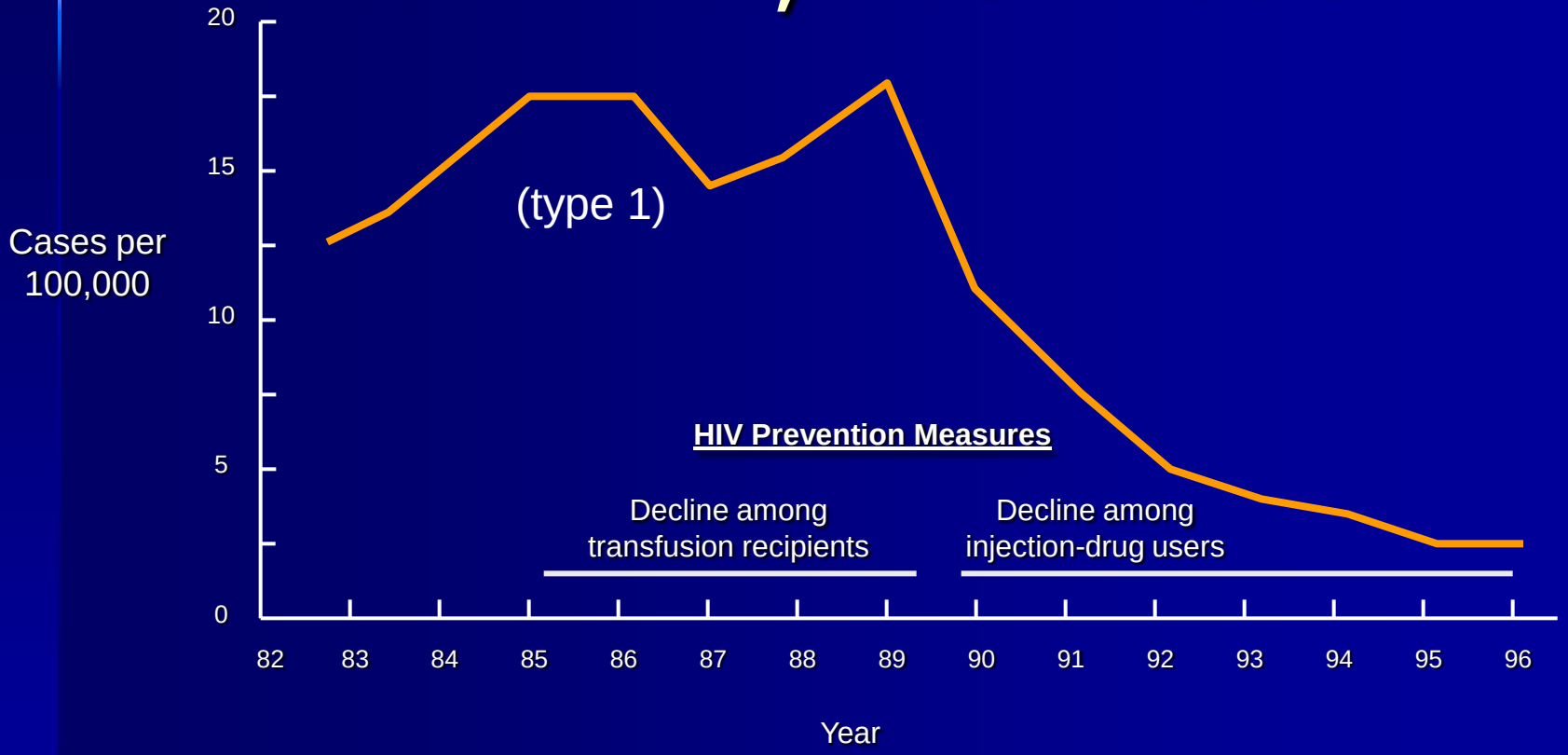
- 1.8% of US population, ~ 4,000,000 (4 times the prevalence of HIV)
  - But up to 30% prevalence in jails and prisons (10 times the prevalence of HIV)
- 1% of population HCV RNA (+), ~ 2,700,000

  Race
  - White 1.5%
  - Black 3.2%
  - Mexican 2.1%
- Highest prevalence in "baby boomers" born 1945-65

CDC. *MMWR*. 1998;47(RR-19):1-39.

Acute Hepatitis C

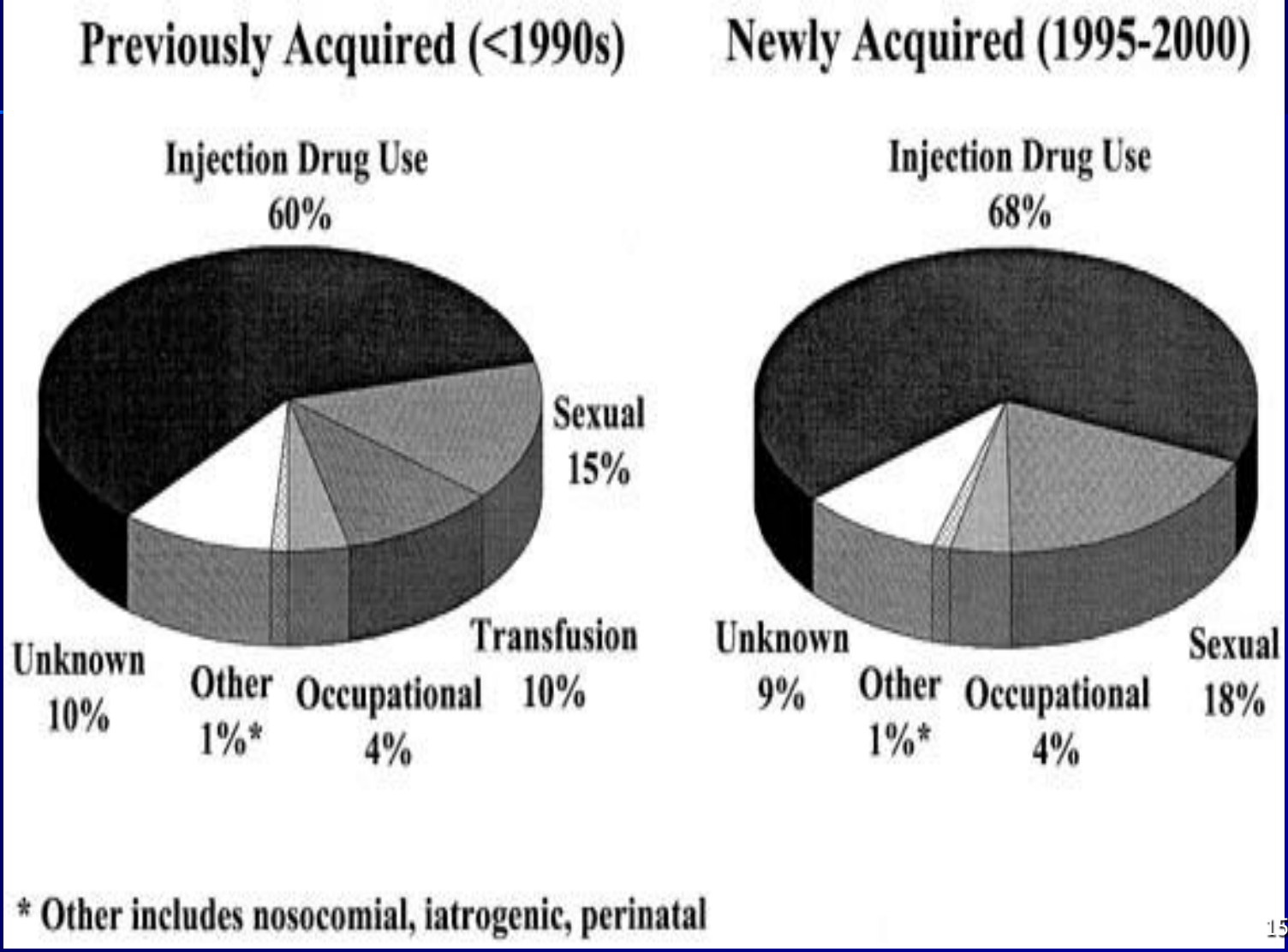
Estimated Incidence, United States, 1982-1996



A cohort of "baby boomers" born 1945-65 have highest prevalence

Centers for Disease Control and Prevention. Unpublished data.

Sources of hepatitis C



Acquisition and Course Of Hepatitis C

- Genotype commonest in the US (type 1) unfortunately worst in prognosis and poorest in responsiveness to treatment
  - Treatment for this type requires 3 drugs
- Approximately 85-90% of infected persons become chronically infected
  - Remainder of infections resolve clinically
  - Unknown if virus is ever totally eradicated
- Course of Hepatitis C variable
  - Severity of illness ranges from transient, self limited and asymptomatic infection to a chronic, progressive liver disease
    - May lead ultimately (usually >20 yrs.) to cirrhosis, HCC,[16] or liver failure

The escalating cost of hepatitis C

- As with HIV, acute infection causes minimal mortality and patients are usually asymptomatic for years
- Serious disease usually takes 20+ years, vs. 10+ for HIV
- Late liver disease will increase as infections mature
  - Cirrhosis
  - Hepatocellular carcinoma (rarely without cirrhosis)
  - Liver failure
- Hepatitis C already leading cause of liver transplants

Prevention considerations

- HIV and hepatitis C have no cures or vaccines
- To prevent transmission, infected persons must reduce partners and likelihood of infecting each partner
- Usually requires behavior change; sometimes, cultural change in an entire community
- Many people will change behavior if they know they are infected, but both infections may be asymptomatic for years
  - People may not know they have been exposed, let alone infected

Prevention considerations, contd.

- Widespread combined screening and partner notification programs for both diseases therefore would seem sensible
  - Mass screening for hepatitis C was not funded till 2013
    - As of 2013, insurance must cover one-time hepatitis C screen for birth cohort 1945-65
  - Some of the funded screening for HIV is anonymous, and most has been limited to HIV alone
  - Partner tracing and notification never implemented for hepatitis C, insufficiently funded in many locations for HIV

The concept of reproductive rate of a disease agent

- To gradually bring a communicable disease into control, the reproductive rate of the infectious agent ($\mathbf{R_o}$) must be less than one.
- $\mathbf{R_o}$ is the number of new cases resulting from each case. $\mathbf{R_o}$ = (average transmissions per exposure) x (exposures/partner) x (partners exposed/time) x (length of time patient is infectious, lifelong for HIV).
- If this number is greater than one, the disease will continue to increase exponentially.

Reproductive rate, contd.

- **Ways to reduce R_o therefore include:**
  - **Reducing infectiousness of sex or drug abuse, by using condoms, or clean needles ("harm reduction")**
  - **Eliminating the behavior that causes exposure, by abstinence, or non-use of injecting drugs (exposure prevention, the truest primary prevention and the topic for another talk)**
  - **Reducing number of persons exposed, by maintaining only monogamous relationships, or non-sharing of needles**
- If the average infected person does not even know s/he is infected until having already transmitted the disease, it is difficult to explain how $\mathbf{R_o}$ can be <1 and current prevention strategy can contain the epidemic.

What else is needed to control transmission of HIV and hepatitis C?

- Communicable diseases are ordinarily controlled at the source (the infected person)
- Direct outreach infected persons ("prevention with positives") has not been linked to case reporting for either HIV and hepatitis C (nor for hepatitis B)
- In the case of HIV, the excuse should not be lack of money, but for hepatitis C, it may be
- Antiviral treatment greatly reduces HIV transmission and might do same for hepatitis

"Prevention with positives"

- "Prevention case management" can assist infected patients to avoid infecting others
  - This can involve treatment adherence, encouraging a sense of responsibility not to infect others, and help with techniques for behavior change
- Partner services (incl. notification) can influence earlier reduction in transmission-prone behavior of persons already infected, help exposed but not yet infected persons to remain uninfected, and lead to earlier treatment
- These services are not routine in most parts of California or other places in U.S.

The Uganda Model: "ABC"

- A program that seems to have been responsible for reduction of unsafe behavior and HIV prevalence in Uganda is known as "ABC." This became a centerpiece of the Global AIDS Bill.
- ***A*** = Abstain from sex if possible
- ***B*** = Be faithful if already involved in a sexual relationship
- ***C*** = Condoms should be used if A and B are not possible.
- No current equivalent for needle transmission (most common for hepatitis C)

Objectives of Beyond AIDS and allied groups

- Eliminate barriers to applying the most effective possible prevention techniques for HIV. e.g.:
  - Confidential reporting by name (battle won 2006)
  - Contact tracing, partner notification, and prevention case management
  - Routine and universal screening
  - Promotion of cultural changes to avoid exposure
    - Not just depending on reducing the harm caused by exposure
  - Devoting resources to diseases in proportion to their importance as public health problems

Objectives of Beyond AIDS and allied groups, contd.

- Eventually, reverse the course of the global HIV pandemic through sound public health policy
- Direct attention and resources to other neglected public health priorities, such as hepatitis C
- Prioritize prevention of transmission

The non-routine nature of HIV testing

- Anonymous testing offered, on assumption that stigma of HIV will deter confidential testing
  - Also, originally, to avoid use of blood bank donations to find out HIV status
- Pre-test counseling was encouraged (and required by law or for funding) until 2006 CDC guidelines changed
  - Still required in California as of 2013
- Written consent required by most states until 2006 CDC guidelines changed
  - Only required in Nebraska, Oklahoma as of 2013

The non-routine nature of HIV testing, contd.

- HIV testing historically has often been deferred in medical settings due to time and skill requirements of counseling
- HIV testing has not been included in routine panels, including for pregnant women in California
- Perception of many patients is that HIV testing is not routine; some may actually be deterred by counseling
- Unique penalties for unauthorized disclosure of results

HIV testing: new technology

- There are now rapid tests, oral and urine tests, and home collection kits to mail specimens to lab
  - No home tests to perform yourself…yet
- November 7, 2002: OraQuick Rapid HIV-1 blood test licensed by FDA
  - 20-minute simple fingerstick test
  - HIV-1/2 version approved March 19, 2004
  - Approved for clinical laboratories
    - Waived CLIA testing approved January 2003 (apparently for HIV-1
  - Does not include confirmatory testing
    - Can keep specimen for confirmatory Western Blot

HIV testing: new technology, contd.

- March 26, 2004: OraQuick Advance, a Rapid HIV-1/2 test approved for oral mucosal fluids (not actually saliva)
  - First approved rapid test not requiring blood
    - Estimated cost to public health clinics $8/test
    - http://www.fda.gov/bbs/topics/news/2004/NEW01042.html
    - http://www.medicineonline.com/reference/Health/Conditions_and_Diseases/Immune_Disorders/Immune_Deficiency/AIDS/info/Rapid-Oral-HIV-Test/
  - Oral Western Blot test also approved for confirmation
  - CLIA waiver approved June 25, 2004
    - http://www.hhs.gov/news/press/2004pres/20040625b.html
  - Urine test exists, but not popular
  - Future: Home testing? Pre-date test kits for two?

HIV testing: new technology, contd.

- What is the difference between saliva and mucosal transudate?

  Oral mucosal transudate has high concentrations of IgG; saliva has practically none. Oral mucosal transudate comes from the tissues of the cheek and gum; saliva comes from the salivary glands.

  – *Information from OraSure*

The OraSure system draws HIV antibodies out of the tissues between the cheek and gum. The virus itself is rarely ever found in oral fluid.

This sample, called mucosal transudate, contains far fewer contaminants than typically found in saliva.

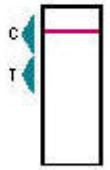
HIV testing: new technology, contd.

http://www.freedomantiviral.com/

HIV testing: new technology, contd.

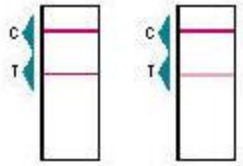
Non-reactive result

- Only control area shows line
- No line in test area



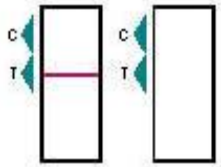
Reactive result

- Control and test lines present
- may not be of similar intensities



Invalid result

- No control line



HIV testing: new technology, contd.

HIV testing: signs of change

- Fall 2002: CDC leadership expresses increasing concern
  - Estimated 200 to 250 thousand Americans with HIV do not know their status
    - Approximately 25%
  - 40,000 new infections/year
    - Despite over 20 years of prevention efforts.

HIV testing: signs of change, contd.

- April 18, 2003 (MMWR): CDC recommends:
  - Unlinking HIV counseling from testing
    - Both still supported but counseling not a prerequisite
  - Making testing routine in medical and other settings.
- 2003: CDC also informally recommending "opt-out" prenatal testing
  - Requires active refusal rather than active written consent
  - Not proposed for other settings at this time

HIV testing: signs of change, contd.

- September 22, 2006: CDC releases revised recommendations on HIV testing of adults, adolescents, pregnant women in health care settings
  - Test routinely in all health care settings
    - At least annually if high risk
  - No pre-test prevention counseling
  - No written consent (the new wrinkle)
    - BUT still required by law in California
    - "General consent for medical care" adequate
    - BUT also states that patient should be notified first and may refuse ("opt-out" screening
  - Prenatally, in routine panel (but also "opt-out" screening)
    - Retest in third trimester if high local rate of HIV in pregnancy

Prevention of HIV transmission to babies: "routine & universal" prenatal testing followed by medication

- 1994: ACTG (AIDS Clinical Trials Group) Protocol 076 study using monotherapy
  - Zidovudine (AZT) can reduce HIV in babies of infected women by two-thirds
- 1998: Institute of Medicine report
  - Advocates routine and universal prenatal testing
  - Notes that counseling can be a barrier
- 2001: PACTG (Pediatric AIDS Clinical Trials Group) Protocol 316
  - Rate of newborn infection can be reduced from over 20% to about 1.5% with combination therapy
  - More recent studies reduced to near zero

The struggle to make prenatal HIV testing more routine in California (3 Beyond AIDS bills)

2003: AB 1676 (John Dutra), similar to two previous unsuccessful bills, became law

- Pamphlet; simple signature for test acceptance
- Still no "opt-out" testing in California, and written acceptance needed
- Bill will make it easier to combine HIV testing with other routine prenatal tests
- Women who miss prenatal testing must be asked to accept test during labor/delivery

New treatment trends for HIV

- Since 1996, treatment based on "cocktail" of 3 or more drugs, known as HAART (highly active anti-retroviral therapy)
- A typical regimen
  - 2 "NRTIs," (nucleoside or nucleotide reverse transcriptor inhibitors) combined with one of the following:
    - protease inhibitor
    - "NNRTI" (non-nucleoside reverse transcriptase inhibitor)
    - More recently: Integrase inhibitor or entry inhibitor

New treatment trends for HIV, contd.

- Earlier regimens involved complex dosages up to 5 times during day
  - Multiple pills, some with food, some without food
- Protease inhibitors are combined with ritonavir (a member of same group) to boost blood levels
- Once daily treatment an advantage
  - Can increase compliance
  - Might slow development of resistance

New treatment trends for HIV, contd.

- Once/day drugs now available
  - NRTI's (Nucleoside and nucleotide reverse transcriptase inhibitors):
    - Videx EC (didanosine/ddI, long-acting capsule)
    - Epivir (lamivudine/3TC)
    - Emtriva (emtricitabine, similar to lamivudine)
    - Viread (tenofovir)
  - NNRTI (Non-nucleoside reverse transcriptase inhibitor):
    - Sustiva (efavirenz)
    - Complera (rilpivirine)
  - PI (Protease inhibitor):
    - Reyataz (atazanavir)
    - Prezista (darunavir) if treatment-naïve
  - Entry inhibitor
    - Selzentry (maraviroc)

New treatment trends for HIV, contd.

- Combination pills
  - Reduce resistance due to noncompliance
    - Strategy previously utilized for TB
  - One pill twice/day combo pill
    - Combivir (zidovudine + lamivudine)
  - One pill once/day combo pills (those highlighted are complete therapy in 1 pill/d)
    - Epzicom (abacavir + lamivudine)
    - Truvada (emtricitabine + tenofovir)
    - Atripla (emtricitabine + tenofovir + efavirenz)
    - Complera (emtracitabine + tenofovir + rilpivirine
    - Stribild (4 components)

New treatment trends for HIV, contd.

- 1996-2000: First concept for use of highly effective drug combinations was to "hit early, hit hard"
- 2001-2011: onset of treatment was delayed till CD4 count decreased (<350, still used internationally; later <500)
  - This change was due to high rate of side effects of early drugs and worry about developing resistance
  - During years of infection before treatment criteria were met, most transmission occurred
  - What was good for public health was not yet known to also be good for the patient

New treatment trends for HIV, contd.

- 2012: Treatment guidelines (U.S. only) reverted to "hitting early"
  - Early and continuous treatment found beneficial to patient outcomes
  - Suppression of viral load found 96% effective in preventing transmission
  - Individual treatment strategy and public health strategy now aligned

Treatment trends for hepatitis C

- **Former Treatment of hepatitis C**
  - **Short-acting interferons requiring 3 times a week (TIW) shots**
  - **Oral ribavirin daily (sold together in Rebetron®)**
- Interferon alpha-2a (Roferon-A®): 3 MU TIW
- Interferon alpha-2b (Intron-A®) 3 MU TIW
- Alfacon-1 (Infergen®): 9 μg TIW
- IFN alpha-2b + Ribavirin (Rebetron®)
  3 MU TIW Pt weight ≤ 75kg: 1000mg
  Pt weight > 75kg: 1200mg

Current treatment: longer acting "pegylated" interferons, weekly shots

- Only the interferon has changed
  - Now long-acting, inject only once/week
  - Still accompany with daily oral ribavirin
- First product:
  - 12 kD Peginterferon alpha 2b (PegIntron®) 1.5 mg/kg injection + Ribavirin 800 mg/day orally
  - **Regimen that received FDA approval**
  - **Higher Ribavirin doses NOT prospectively studied nor FDA approved**

Current treatment for hepatitis C, contd. – latest product pair

- 40 kD Peginterferon alpha 2a (Pegasys®)
  - 180 mcg sq weekly

+ Ribavirin (Copegus®)

≤ 75kg, 1000mg/d

>75 kg, 1200mg/d

Current treatment for hepatitis C, contd. – New drugs as additives

- Add a third drug to pegylated interferon and ribavirin for genotype 1
  - Ages 18 and over
  - Boceprevir (Victrelis, approved 5/13/11): 800 mg tid (q 7-9 hrs) with food, add from wk 4 to wk 28 of interferon-ribavirin treatment
    - Duration depends on viral RNA monitoring
  - Telaprevir (Incivek, approved 5/23/11): 750 mg tid (q 7-9 hrs) with food, 1st 12 wks of treatment
    - Follow with only 12 more weeks of other 2 drugs

Coming treatment for hepatitis C

- Oral drug combinations, IFN and ribavirin-free, are eagerly awaited by patients and providers
- 26 drugs being studied, several promising drugs in pipeline, 2 approved
  - Simepravir (Olysio) approved 11/25/13
  - Sofosbuvir (Sovaldi) approved 12/6/13
  - Both once/day; not yet approved for HIV-coinfection or for use without interferon

Treatment problems

- All current treatments for both HIV and hepatitis C are very expensive and have significant toxicity
  - Antiretroviral drugs cause GI side effects, anemia, rash, fat redistribution (lipodystrophy), pancreatitis, neuropathy, hyperlipidemia, even diabetes
    - Sometimes hard to tell which drug is responsible, because used together and HIV alone can cause some of these effects
  - Interferon causes flu-like symptoms, neutropenia, thyroid problems, depression, even suicide; ribavirin causes hemolytic anemia and birth defects requiring **2 methods** of contraception

Treatment problems, contd.

- Drugs are needed that are active against both HIV and hepatitis C
  - Lamivudine and tenofovir are active against both HIV and hepatitis B (so is adefovir, though withdrawn for HIV), but no drugs currently help both HIV and hepatitis C.
  - Protease inhibitors, a class in which some drugs work for HIV, are now being applied for hepatitis C.

Initiatives by private industry

- In Africa, pharmaceutical companies (stung by criticism for high drug costs) collaborating with NGOs (non-governmental organizations) to fund programs for treatment
- Pharmaceutical companies reducing prices on drugs for third world
  - Waiving patents to permit local manufacture of generics
- In absence of adequate funding for hepatitis C prevention, pharmaceutical companies (e.g., Schering, Roche) have been a key source of educational materials

Conclusions:

- HIV and hepatitis C are both difficult to control and difficult to treat
  - Neither is curable and neither has a vaccine
  - Both are immense public health problems.
- Public health efforts are hampered by
  - Political restrictions (especially for HIV)
  - Lack of funding (especially for hepatitis C)
- New strategic approaches and new treatment strategies have recently been developed which are expected to benefit patients and reduce transmission
- Both diseases need a "continuum of care" to detect and treat infected persons