THE ROLE OF THE LABORATORY IN HIV PREVENTION

Harold Jaffe, M.D.
Centers for Disease Control and Prevention, Atlanta, GA
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First, I am going to discuss some important new and exciting trends in the HIV/AIDS epidemic in this country. Next, I will try to point out areas where I believe the laboratory has an important role to play in HIV prevention. Finally, I will give some specific examples of ways in which the laboratory is playing this role.

My CDC colleague, Dr. Kevin DeCock, provided this slide (Slide 1) as a way to look at both the epidemiology of HIV/AIDS and prevention opportunities. This schematic first depicts the incidence of new HIV infection, that is the number of new infections per year, as a spigot, which fills up a reservoir. The prevalence of HIV infection, or the proportion of persons who are infected, is measured by the height of the water in the reservoir. As these infected persons become immunosuppressed and start developing AIDS-defining conditions, they exit through another spigot, representing the incidence of AIDS, and fill another reservoir, the level indicating the prevalence of AIDS. And finally, some of these persons exit this reservoir through another spigot, as they die from AIDS. Each of these spigots represents a prevention opportunity in the sense that by closing these spigots we prevent progression to AIDS and death.

You have undoubtedly heard of the very dramatic decreases in the incidence of AIDS cases and deaths over the last several years, trends that are shown in the next few slides.

(Slide 2) This overview slide shows the estimated incidence of AIDS cases and deaths in adults and adolescents, adjusted for reporting delays, from 1985 through September 1997. The top line shows AIDS cases reported per quarter, which peak in 1993, followed by a gradual decrease. Even more striking is the lower curve, showing a dramatic drop in AIDS deaths, starting in late 1995 and continuing into 1997.

(Slide 3) These changes are more clearly demonstrated in the next couple of slides, which compare the first nine months of 1997 with the same period in 1996. The overall decrease in reported cases from 1996 to 1997 is about 14%, but varies considerably by patient group. Although decreases are seen in all patient groups, the decreases are greater for men than women, for whites than for African Americans and Hispanics, and for men who have sex with men than for injecting drug users or persons infected through heterosexual contact.

Slide 4 shows similar depiction of the drop in AIDS deaths over the same period. The change is even more dramatic, with a 44% drop in AIDS deaths over a single year, but again, more favorable trends for men, white persons, and persons infected through male homosexual contact. Once again, these are changes that occurred over a one year period.

These favorable trends may be the result of one or more "upstream" changes, including decreases in the incidence of HIV infection and/or a slowing in either progression from HIV infection to AIDS or from AIDS to death. As I will discuss shortly, we lack accurate data on recent trends in HIV incidence, but we have good data to indicate that improved antiretroviral therapy and the use of antimicrobial prophylaxis and vaccinations to prevent opportunistic

infections are clearly slowing the rate of HIV disease progression.

A good source of information on the effect of these interventions on disease progression is the Adult Spectrum of Disease Study (ASD), a multicenter study funded by CDC, in which the charts of over 20,000 HIV-infected persons are reviewed every 6 months.

Slide 5, from the ASD study, looks at the overall effect of several types of intervention on progression from HIV infection to death. The data are shown as risk ratios. The lower the risk ratio, the lower is the rate of disease progression. The effect of each intervention is adjusted for the effect of other interventions. Antiretroviral therapy, monotherapy, dual-therapy, and triple-therapy (showing a very dramatic impact) are slowing the rate of disease progression, particularly when we see combinations of two or three drugs. Adjusting for the use of antiretroviral therapy, we can then look at the impact of specific prophylaxis for particular opportunistic infections. For example, the use of sulfatrimethatrine to prevent pneumocystis does have an impact, though not as dramatic as antiretrovirals. There are also more modest benefits associated with the use of prophylaxis for Pneumocystis pneumonia and Mycobacterium avium infections, and with administration of the pneumococcal vaccine.

The ASD study also gives some insight into why morbidity and mortality trends have been more favorable in some groups, such as gay men, than in other groups, such as injection drug users (IDUs). First, gay men received more care, with a median of 9 outpatient visits per year compared to 6 visits for IDUs. Second, the gay men were more likely to receive combination antiretroviral therapy, defined as 2 or more antiretroviral drugs. In 1996, about half of the gay men were on combination therapy compared to less than a third of the IDUs. And third, the gay men were more likely to receive recommended antimicrobial prophylaxis than the IDUs, such as the drugs recommended for M. avium prophylaxis. Gay men are more likely to be prescribed these medications than IDUs. Compliance with prophylaxis was not assessed in the study, but it could also be a contributing factor.

So far, we have only been discussing trends for adults and adolescents, but the news regarding AIDS in children is also good. Slide 6 shows perinatal AIDS cases, that is, cases resulting from mother-to-child HIV transmission, decreased by 42% from 1984 through 1997, peaking in about 1992. Since we believe that the number of HIV-infected pregnant women has not dramatically decreased, we believe these trends result from the use of antiretroviral therapy in pregnant women to reduce the rate of perinatal transmission. Initially, treatment of pregnant women was limited to zidovudine monotherapy, but in the last several years pregnant women have been receiving the same combination therapies used for all other adults.

So for both adults and children, the message is clear: If our goals are to prevent HIV infected adults from progressing to AIDS and death and to prevent HIV-infected pregnant women from transmitting infection to their children, we must identify infected persons as early in the course of their disease as possible, and we must offer them care. How well are we doing that, and how can the laboratory help us do a better job?

Overall, it appears we are not doing a great job in identifying infected persons. In this study by Pat Sweeney and her colleagues from the CDC, it is estimated that of the approximately 650,000-900,000 infected Americans, about 500,000 - 550,000 or roughly two-thirds, have been confidentially tested for HIV. Although additional infected persons may have been tested anonymously for HIV and know their infection status, it seems clear that about one third of infected Americans still do not know they are infected.

It also appears that when persons are tested, it is often relatively late in the course of their infection. Dr. Pascale Wortley and associates from the CDC examined the patterns of HIV testing for persons reported with AIDS from 1990 through 1992. Although the study is rather old, it makes some important points. This is a study beginning with people who have AIDS and asking them about when they were tested for HIV infection and how they were tested for HIV infection. First, about two-thirds of persons with AIDS had their initial positive HIV test done in acute health-care settings, including hospitals, physician offices and emergency departments, suggesting that they may already have been ill when the test was done. Only 13% of these persons were tested in HIV testing and counseling sites. Second, data on the reason for testing confirms that over half of the patients were tested because of illness. And thirdly, about half these patients had their first positive test within a year of their AIDS diagnosis, with about a third tested within 2 months of the diagnosis. For many of these persons, testing was done too late to prevent them from developing an AIDS-defining illness. The challenge, then, is to test and identify these infected persons before their disease has progressed.

(Slide 7) Unfortunately, because of delays that are inherent in our current HIV testing algorithms, even when persons at-risk for infection are tested, they may not receive their test results. Dr. Katie Irwin from the CDC and her collaborators undertook a study at Bronx-Lebanon Hospital Center, a general hospital in New York City with one of the highest prevalences of HIV infected patients in the United States. Patients between the ages of 18 and 44 were offered testing if they were not known to be HIV infected or have AIDS and were either inpatients or seen in the emergency room. About half of the patients consented to testing and those patients were then told to return in 2-3 weeks for their test results. Of the 837 patients who were tested, 5.4% were found to be infected. Rates of return for test results were 63% for emergency room patients and 55% for inpatients. About a third of the 45 patients who were infected never received their results. If rapid testing had been available, these patients could have at least have been given a preliminary result and those found to be positive could have been encouraged to return to receive a confirmed result.

Dr. Bill Kassler and associates took this approach one step further and evaluated the use of the SUDS test, the only rapid test licensed in the United States, to screen for HIV infection in both an anonymous HIV testing clinic and a sexually transmitted disease (STD) clinic in Dallas, Texas. At both of these sites, the SUDS test with same day results was made available for a three week period in 1993. Results of testing during the period when the rapid test was available were compared to a previous interval when testing was only available using the standard Enzyme Immunoassay (EIA) and Western blot (WB). Non-reactive SUDS results were reported as negative, while reactive results were reported as a "preliminary positive," and these patients were then scheduled to return for Western blot results. A number of testing parameters from this three week period of rapid testing were then compared to a previous three week period in which testing was only available through a conventional EIA/WB algorithm. During the period of conventional testing, patients were told to return back to the clinic two weeks later to get their test result.

(Slide 8) This slide compares results of testing done by the standard and rapid protocols in the anonymous test clinic. HIV prevalence was 2.4% during the time that standard testing was done and 3% during the rapid testing period. With implementation of rapid testing, the proportion of clients who received their negative test result rose from 95% to 99%. Even more striking, the proportion of infected clients who received their test results rose from 86% to

100% with rapid testing. Since persons who had positive SUDS tests had to return to receive a WBconfirmed result, this indicates that all such persons returned to receive the confirmed result.

(Slide 9) In the STD clinic, where the primary purpose of a patient visit is related to STD care rather than HIV testing, the results are even more impressive. With rapid testing, the proportion of persons receiving negative results rose from 30% to 93%, while the proportion receiving positive results increased from 79% to 97%. In contrast to the anonymous test clinic, the STD clinic retains patient name and locating information, so it is possible for clinic staff to attempt to locate non-returning infected patients and provide them with their test results. With the standard testing protocol, 34% of infected persons received their results only after a field follow-up visit, an expensive and time consuming procedure. However, field follow-up was needed for only 3% of infected persons who screened positive by the SUDS test. In other words, provision of preliminary positive results based on rapid testing seems to motivate patients to return for a confirmed test results.

Initially, there was a lot of anxiety among Dr. Kassler's staff about using the rapid testing and how patients would react to it. However, the response was quite favorable. A survey of 225 clients who had rapid testing done at either the anonymous test site or STD clinic showed a high level of satisfaction with this method of testing. Most clients indicated they understood the meaning of rapid tests results, and about 80-90% said they would prefer getting a rapid test result during their initial clinic visit rather than having to return to receive a conventional test result. Although counselors at these clinics were initially concerned about the rapid testing method, a survey done after a month of experience with the rapid test indicated that some clients who received preliminary positive results followed by a confirmed results felt this method reduced stress by breaking the news gently.

(Slide 10) Dr. Bernie Branson from the CDC has taken the results from this Dallas trial and used them to model the impact of applying rapid testing to the publicly funded testing programs conducted in the United States. Over two million HIV tests are done in these programs every year. However, in 1995, 25% of infected persons and 33% of uninfected persons did not return to receive their test results. The top part of this slide shows HIV prevalence by test site and the rates at which clients return to receive results obtained by the conventional testing algorithm . Similar to what was seen in the Dallas study, return rates were highest in the counseling and testing sites where clients are specifically requesting testing and lower in other testing sites, especially in STD clinics. Dr. Branson found that if the experience in the Dallas STD clinic can be generalized to these other sites, national implementation of rapid testing might increase return rates to 97% for positive results and 93% for negative results.

(Slide 11) In this slide, Dr. Branson summarizes his estimate of the overall impact of rapid testing in all publicly funded test sites. Compared to the current testing algorithm, rapid testing allows an additional 8,000 infected persons to receive their test result, an increase of 29%. Since most clients at these facilities are uninfected and uninfected persons often do not receive their results under the current testing algorithm, rapid testing has a big impact in this group, increasing the number of persons receiving a negative result by almost 700,000 or 50%. The downside of the rapid testing is also shown on this slide, with about 8,000 patients receiving a false positive. These patients will not know the results are false positive until they return for their Western blot result. Even though these patients would have been informed that their screening test might be incorrect, they may suffer unnecessary anxiety while waiting for confirmatory testing to be completed.

One way to minimize the problem of false-positive rapid screening tests is to use them in populations where the prevalence of infection is relatively high. As with all other tests, the positive predictive value of a rapid HIV test increases with the prevalence of HIV infection. Given the performance characteristics of the SUDS tests, a sensitivity of 99.3%, and specificity of 99.5%, the positive predictive value increases from only 50% in a population with 0.5% prevalence of HIV infection to over 90% in a population with 5% seroprevalence. Thus, if rapid testing is used for screening, it will probably be most beneficial in settings of high prevalence in which a low percentage of persons usually return for their test results.

Rapid testing may also find application in some other settings where it is necessary to make immediate decisions about initiating prophylaxis for an HIV exposure. For example, rapid testing could be considered for pregnant women who are thought to be at increased risk for HIV and who present in labor with no previous HIV test result available. If the woman tests positive, she could be given intrapartum antiretroviral therapy and her newborn could be treated, pending the results of confirmatory testing. Another example would be testing the source patient of an occupational HIV exposure. Post-exposure prophylaxis could be offered to a health care worker (HCW) exposed to the blood of the source patient who tests positive, with the understanding that prophylaxis could be stopped if additional testing fails to confirm the screening test result. A final example would be testing potential organ donors before their organs are harvested.

CDC studies have indicated that if two rapid tests are used sequentially, they can give results that are comparable to the EIA/WB algorithm. If additional rapid tests are licensed in the United States, it would be theoretically possible to give a patient a confirmed test result during an initial clinic visit. However, operational and behavioral research questions would need to be answered before this approach could be considered for widespread application. For example, how long would it take to do sequential rapid testing? Also, we must find out if patients are emotionally prepared to receive a confirmed result after their first visit, particularly if the primary purpose of their visit was for something other than HIV testing.

If we are successful in identifying more infected persons and referring them for treatment, an additional goal is to be reasonably confident that the treatment will be successful. Based on guidelines published by the U.S. Public Health Service most infected persons should be offered antiretroviral therapy. But as discussed by Rob Schuurman and Robert Coombs, emerging viral resistance may render treatment ineffective. I would therefore like to briefly describe how the CDC is attempting to develop a surveillance program to monitor HIV antiretroviral resistance in the United States.

In the program that we have begun, three sentinel populations are being monitored. First, we are monitoring recently infected persons as a measure of the prevalence of resistance in untreated persons. Second, we are studying pregnant women and their infants to determine if these women harbor viral strains that are resistant to the antiretrovirals commonly prescribed during pregnancy and if resistant strains are being transmitted to their infants. Third, we are interested in the resistance patterns of strains to which healthcare workers are occupationally exposed.

The methods being used in this surveillance system continue to evolve, but the genotypic methods now being evaluated include gene chip hybridization-based sequencing, direct solid phased sequencing, and point mutation probe assays. The phenotypic resistance assays include conventional culture-based assays, novel assays for detecting drug resistant reverse transcriptase activity in plasma by the Amp-RT

method, and evaluation of recombinant virus assays.

Our hope is to establish a surveillance system to allow us to monitor resistance in the same populations over time. Whether data on the prevalence of resistance will help guide initial therapy remains to be seen, although that is certainly the case for other infections of public health importance, such as gonococcal, pneumococcal, and mycobacterial infection resistance patterns.

So far, I have largely discussed secondary prevention; i.e., the prevention of morbidity and mortality in HIV-infected persons. But what about primary prevention, prevention of HIV infection itself? Although a number of primary prevention approaches are being tried at a national level, it has been difficult to measure their direct impact in decreasing the incidence of HIV infection. Let us first review existing surveillance tools that are being used to measure HIV incidence.

(Slide 12) One way to make incidence estimates is to examine the rate of new infections among persons who make repeat visits to clinics that are part of the CDC's national serosurveillance network. All states require that persons meeting the AIDS case definition be reported, and about half of them require that people with HIV infection who have not yet developed AIDS be reported as well. For example, this map shows HIV prevalence among gay men attending STD clinics in 1996, where rates ranged from about 4% in Minneapolis to 30% in Houston.

(Slide 13) By testing persons who make repeat visits to these clinics, it is possible to estimate their incidence of infection, expressed as the number of infections per 100 person years of follow up. For repeat attendees at the STD clinic, infection rates are much higher for gay men than for heterosexual men and women at all study sites. However, incidence estimates based on testing repeat attendees are biased because only a subset of patients make repeat visits. To avoid the bias, we need a way to estimate incidence without requiring repeat visits.

Recently, Rob Janssen from the CDC, Sue Strainer, from Abbott Laboratories, Mike Busch, and others called the Sensitive/Less Sensitive Testing Group published a novel approach to this problem. The goal of HIV testing is usually to make the antibody tests as sensitive as possible, allowing us to detect recently infected persons. But is it also possible to modify the tests to make them less sensitive? A person who is positive by a sensitive assay but negative by a less sensitive assay has most likely been recently infected. By knowing the proportion of all infected persons in a population that are recently infected, one can then model the incidence of infection in that population.

(Slide l4) For the purposes of this study, the Abbott 3A11 whole virus lysate HIV-1 EIA was made less sensitive by increasing the sample dilution and decreasing incubation times. The effect of this modification was an increase of about 4 months in the time needed to detect seroconversion following infection. Again, a person who is seropositive by the sensitive assay and negative by the insensitive assay is likely to be in this period of early infection.

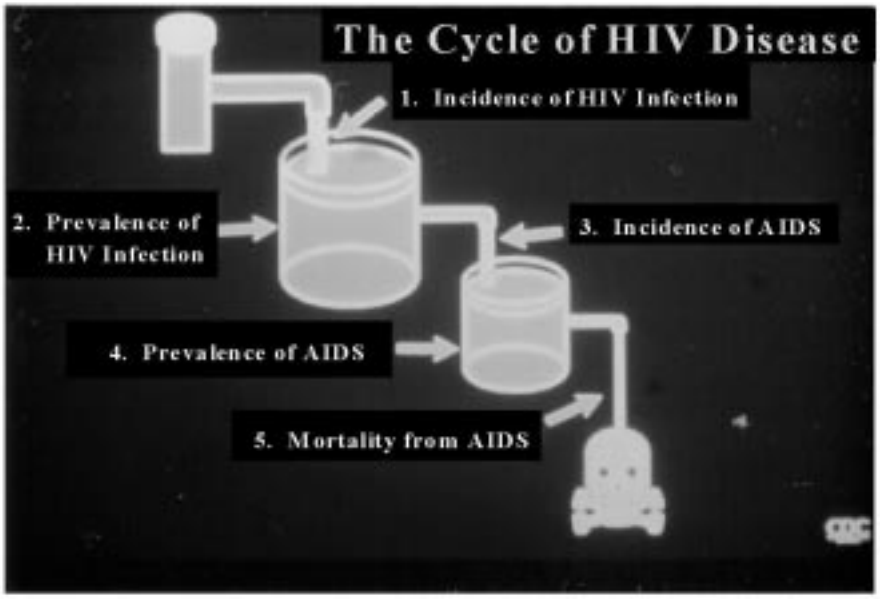
(Slide 15) Based on this approach, how well can incidence be modeled? Here are examples of two studies, one of gay men in San Francisco and the other of blood donors, in which the observed incidence of HIV infection is compared to the estimated incidence derived from the use of the Sensitive/Less Sensitive Testing Strategy. In both cases, the estimated incidence is remarkably close to the observed incidence.

Our hope is that this strategy can be applied to other populations as well. Use of this strategy would give us a very good measurement of the effect of prevention efforts. Beyond its use to estimate HIV incidence, identification of recently infected persons may help in partner

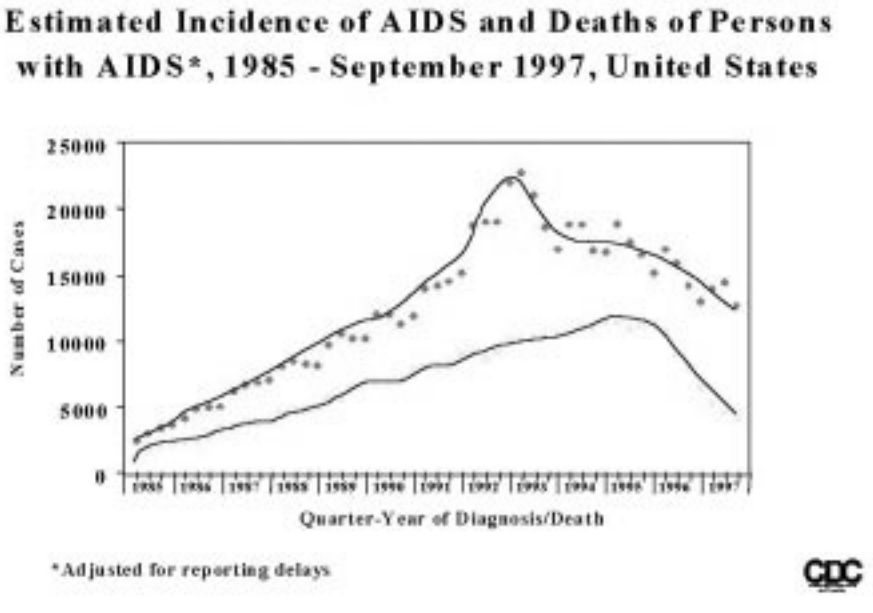
notification efforts, and recruitment of subjects for studies of early treatment.

In summary, we see the laboratory playing key roles in identifying HIV-infected persons, determining the susceptibility of their HIV strains to antiretroviral agents, and monitoring the effectiveness of HIV prevention efforts. Through these varied roles, the laboratory can help decrease the rate of new infections and help assure that infected persons will live longer and better lives.

Slide 1



Slide 2



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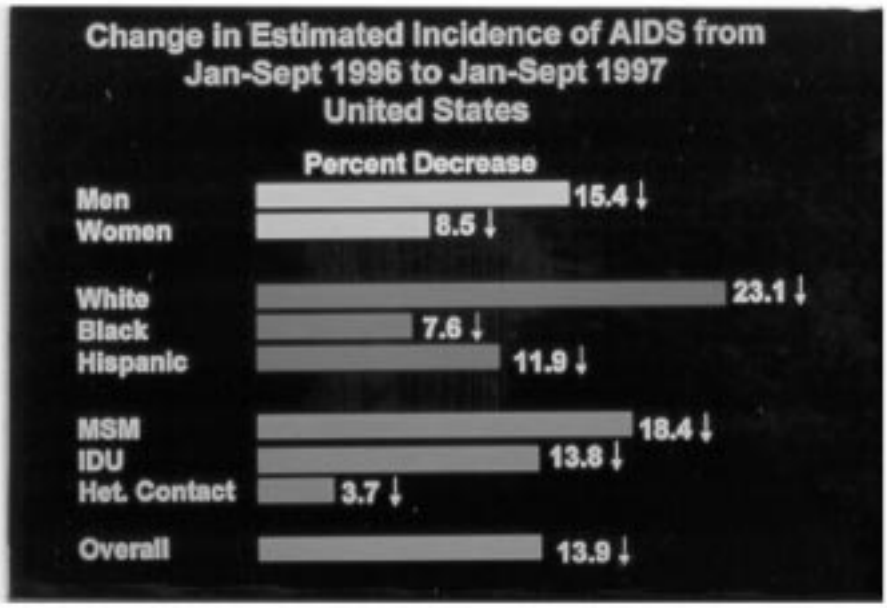

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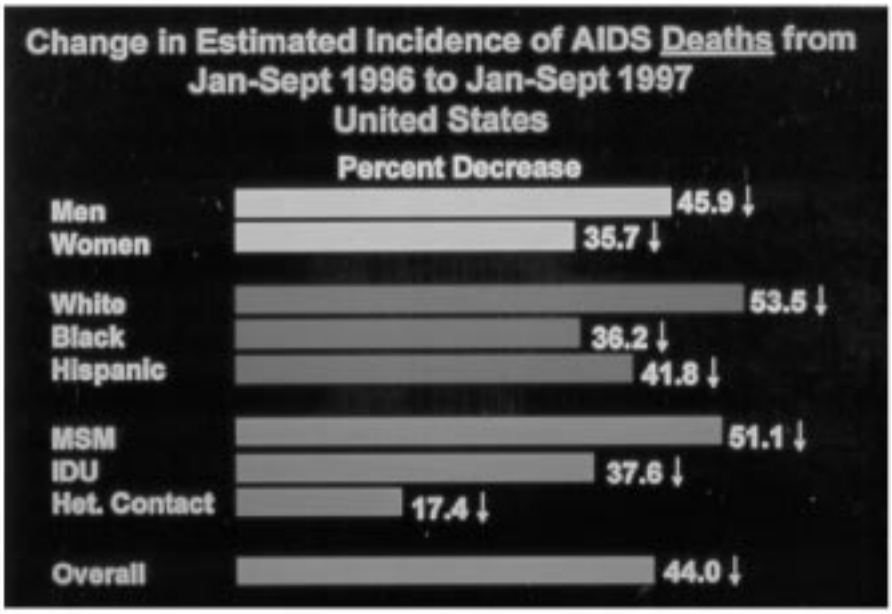

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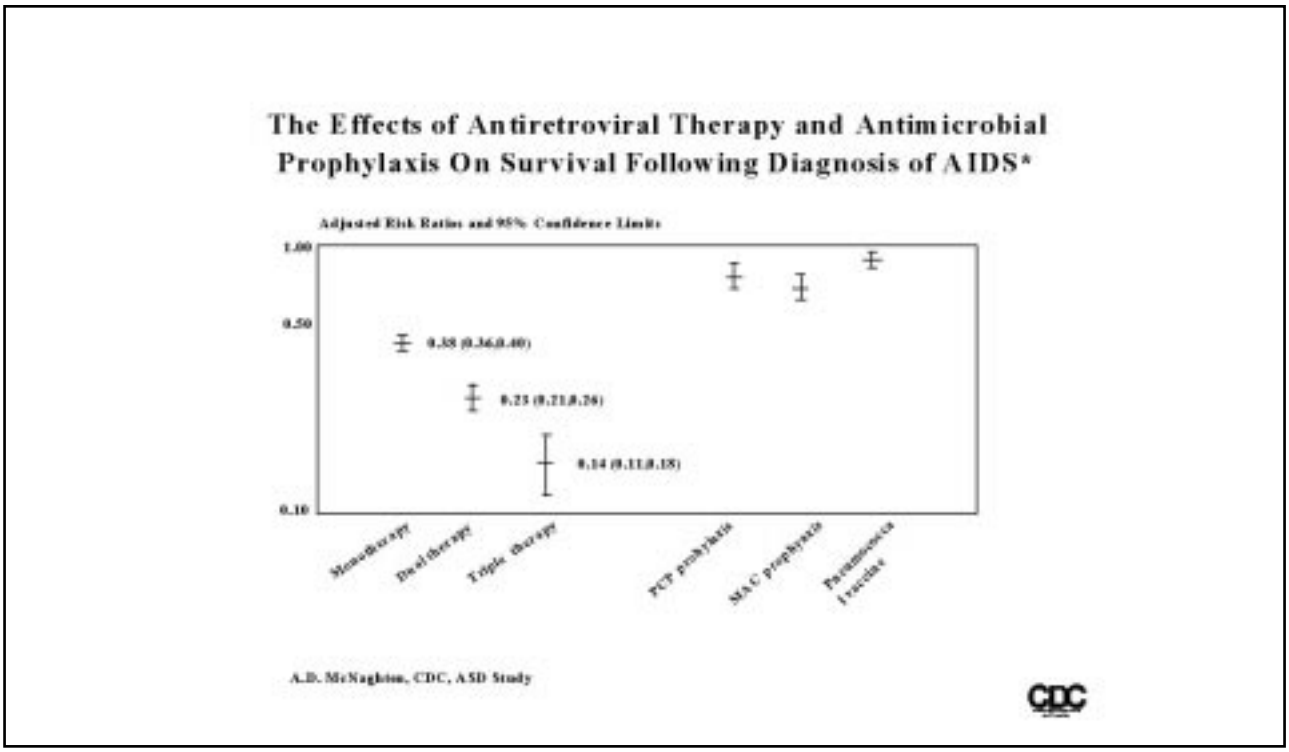

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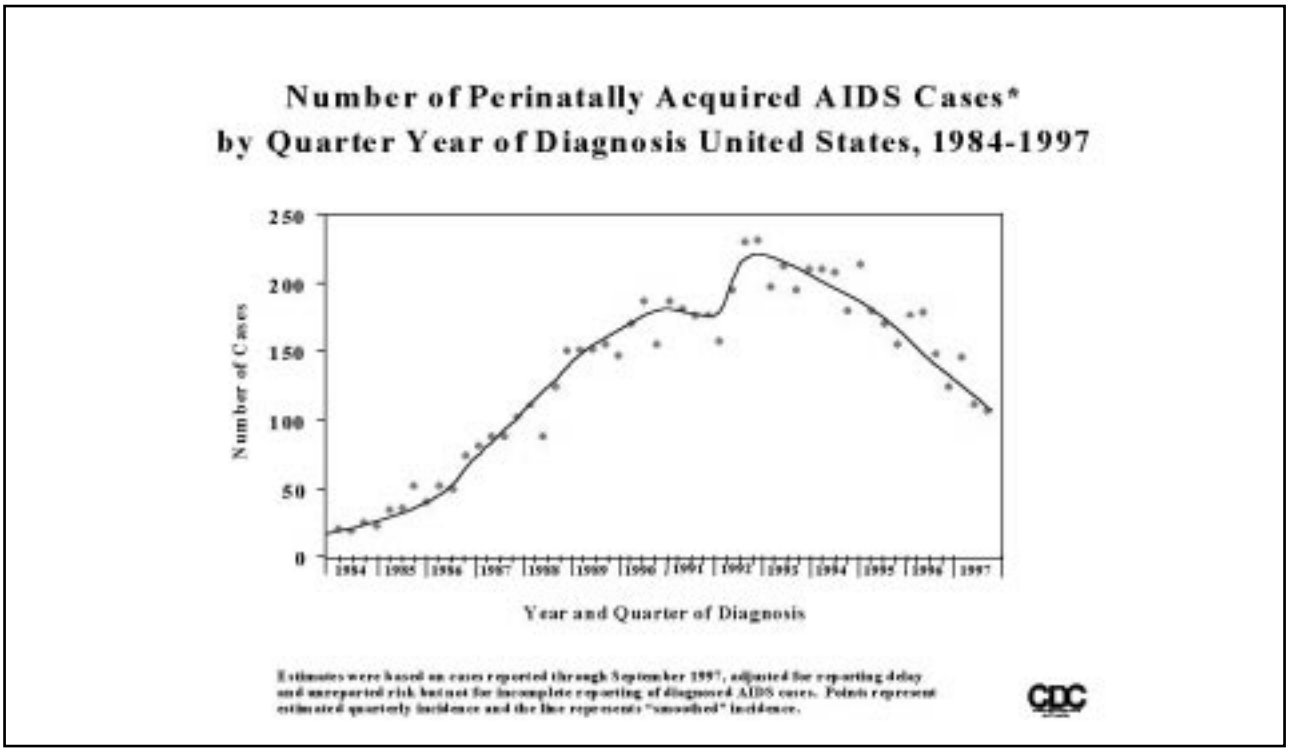

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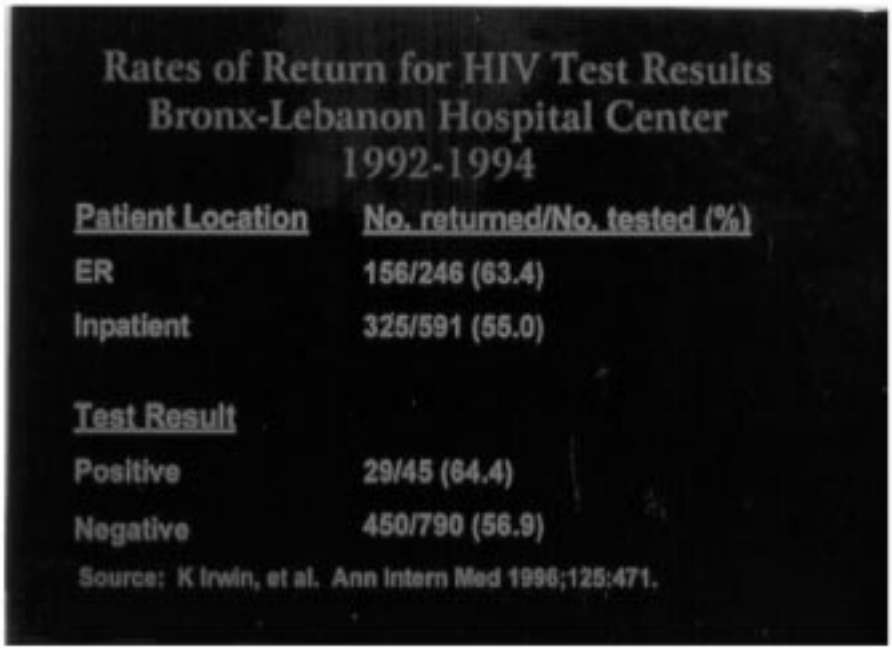

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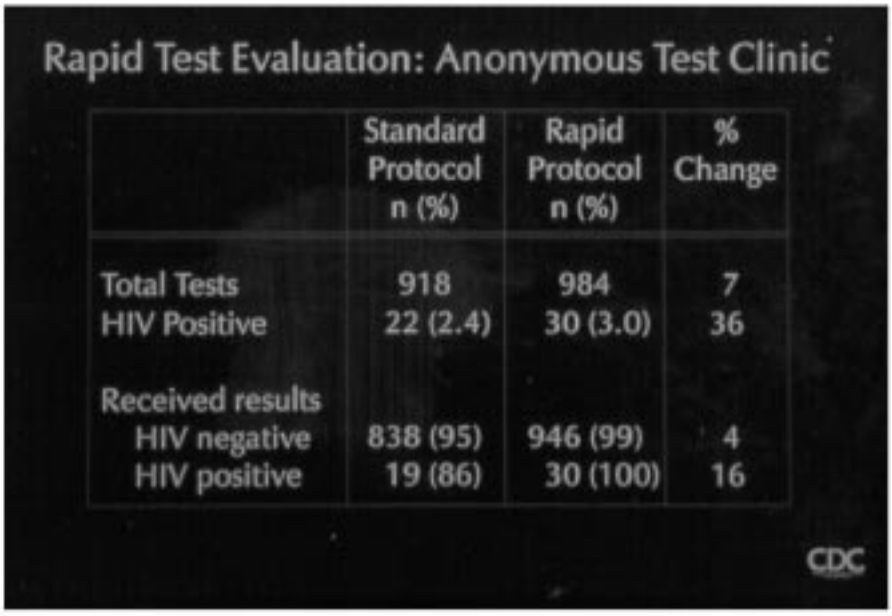

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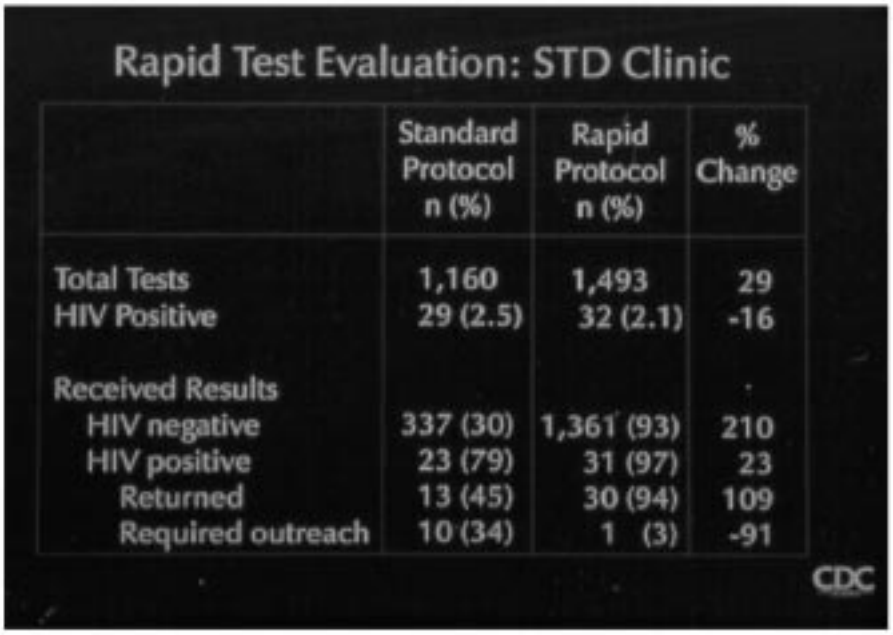
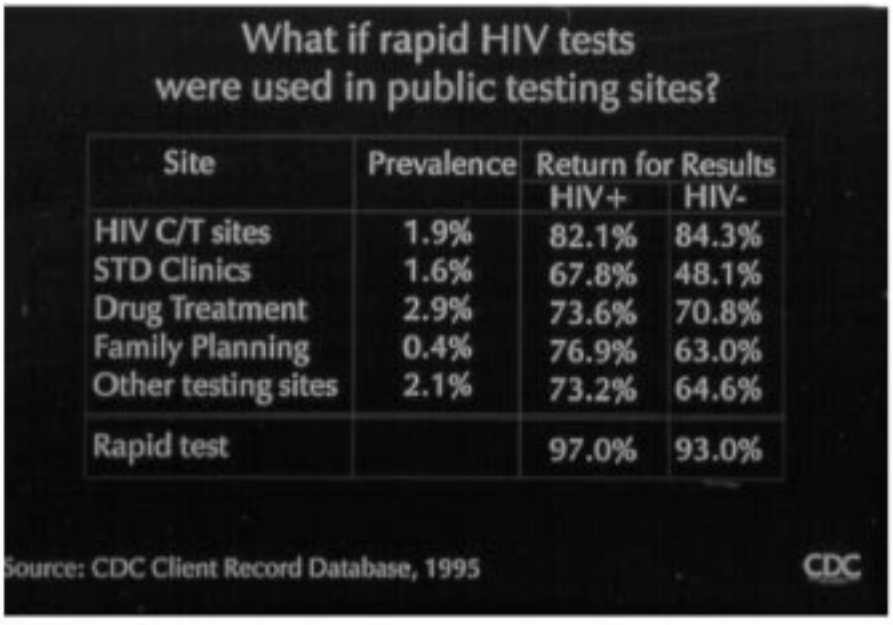


Rapid Test Evaluation: STD Clinic

	Standard Protocol n (%)	Rapid Protocol n (%)	% Change
Total Tests	1,160	1,493	29
HIV Positive	29 (2.5)	32 (2.1)	-16
Received Results			
HIV negative	337 (30)	1,361 (93)	210
HIV positive	23 (79)	31 (97)	23
Returned	13 (45)	30 (94)	109
Required outreach	10 (34)	1 (3)	-91

CDC

Slide 10



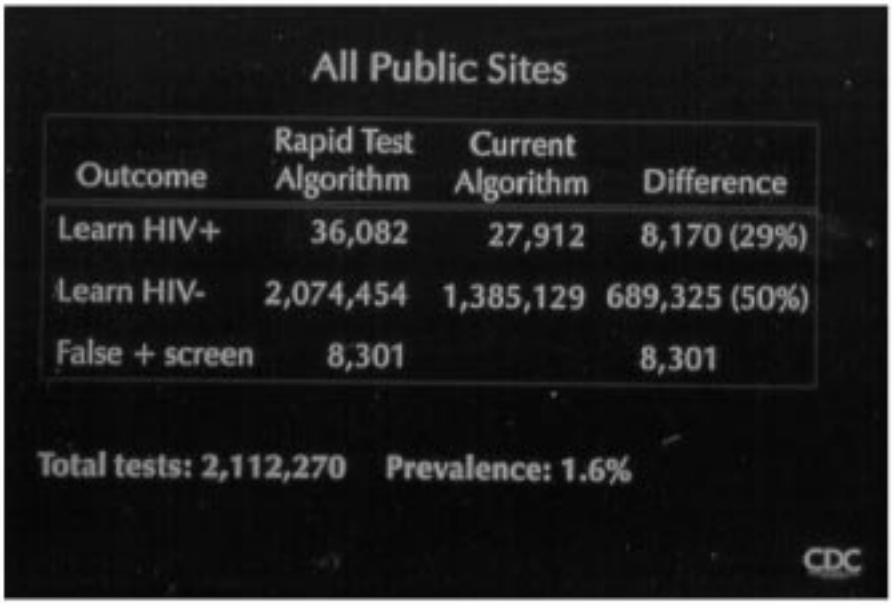
What if rapid HIV tests were used in public testing sites?

Site	Prevalence	Return for Results	
		HIV+	HIV-
HIV C/T sites	1.9%	82.1%	84.3%
STD Clinics	1.6%	67.8%	48.1%
Drug Treatment	2.9%	73.6%	70.8%
Family Planning	0.4%	76.9%	63.0%
Other testing sites	2.1%	73.2%	64.6%
Rapid test		97.0%	93.0%

Source: CDC Client Record Database, 1995

CDC

Slide 11



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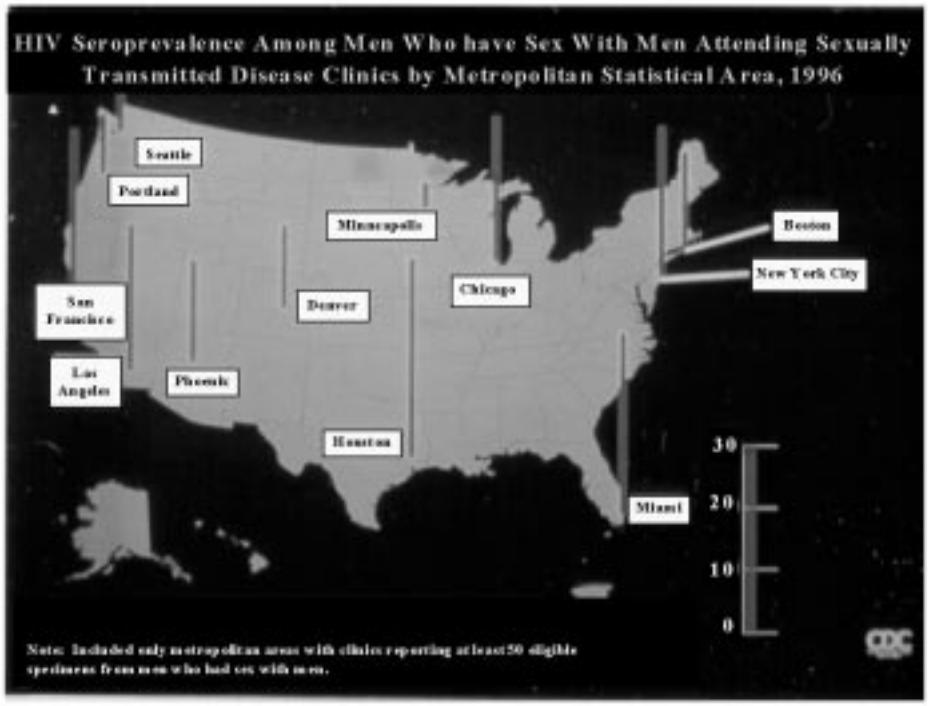

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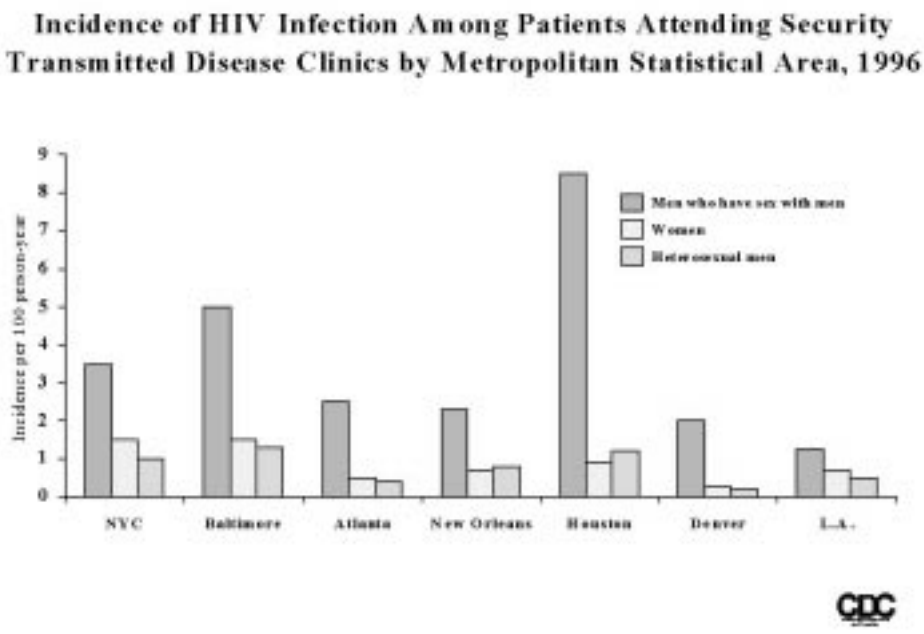

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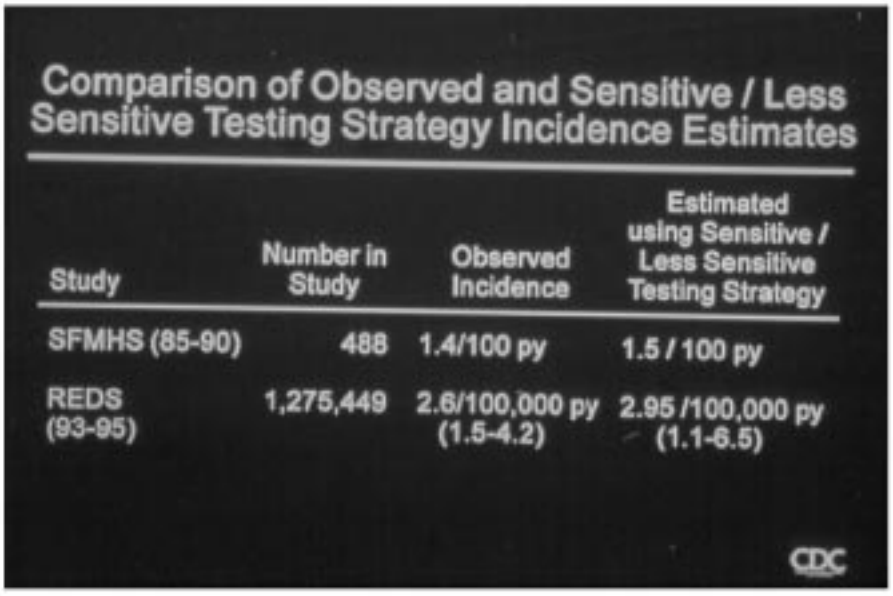

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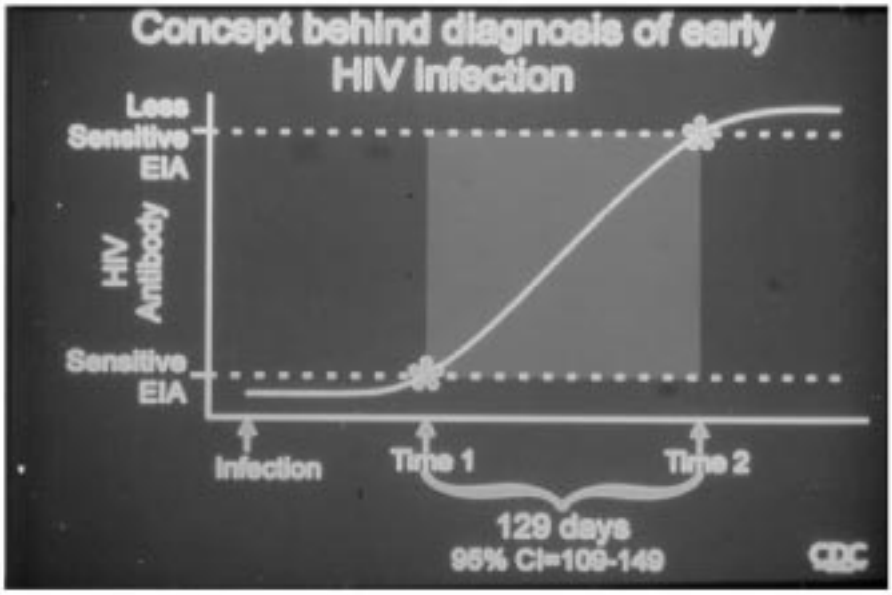
Concept behind diagnosis of early HIV infection
Less Sensitive EIA
HIV Antibody
Sensitive EIA
Infection
Time 1
Time 2
129 days
95% CI=109-149
CDC