



Beyond the end of exceptionalism: integrating HIV testing into routine medical care and HIV prevention

Rachel Smith, Nicola M Zetola and Jeffrey D Klausner[†]

In September 2006, the US CDC issued new guidelines for HIV testing. These guidelines were designed not only to simplify and expand HIV testing but to integrate testing into routine medical care in the USA. The nationwide implementation of these guidelines is currently facing several political and legal barriers. In this article, we examine the origins of current patient-driven and risk-based HIV testing in the USA and highlight shortcomings of this strategy. We then demonstrate how the changing HIV epidemic in the USA requires routine HIV screening at all points of contact in the medical system in order to control the HIV epidemic and how novel testing strategies could increase the yield of testing in these settings.

Expert Rev. Anti Infect. Ther. 5(4), xxx–xxx (2007)

When the US CDC reported on five men with *Pneumocystis carinii* pneumonia in June 1981 [1], no one could have foreseen the devastating impact and the great public health challenge of the HIV pandemic. Since then, advances in biology have elucidated how the virus functions and replicates, diagnostic testing has improved and multiplied in type, and antiretroviral treatment has changed the face of the epidemic by providing the first effective means to treat HIV infection. Through these efforts, deaths due to HIV infection in the USA have declined sharply, an astonishing feat [2]. However, continued disease surveillance demonstrates that there is still much work to be done.

Today, 25 years after that CDC report, there are an estimated 65 million people living with HIV worldwide [3] with 1.2 million in the USA [4]. Over the last 25 years, HIV has claimed the lives of over 22 million people worldwide and more than 500,000 people in the USA alone [4]. Despite great efforts to prevent the spread of the disease, the annual number of new HIV/AIDS cases and HIV-related deaths in the USA has remained at 40,000 and 16,000, respectively, since 1998 [5]. Recent prevalence data suggest both a

resurgence of the disease in traditional risk groups, as well as rising incidence of HIV infection in other populations. Men who have sex with men (MSM) still make up a majority of newly diagnosed HIV infections [3]. However, heterosexual transmission is on the rise, as well as HIV prevalence in members of racial and ethnic minority groups. In 2004, the CDC reported that the rate of HIV diagnosis among African-Americans was 8.4-times that of whites [6]. Additionally, an estimated quarter of people living with HIV infection in the USA (252,000–312,000) do not know they are infected [7]. These people, unaware of their serostatus, are thought to account for 50–70% of new sexually transmitted HIV infection [8]. Furthermore, approximately 40% of newly diagnosed HIV-infected individuals in the USA are diagnosed late in the course of disease, many of whom belong to populations traditionally not considered to be at risk for HIV infection [9–11].

The rising prevalence of HIV infection, the large population of people unaware of their HIV infection and the unacceptably high number of individuals diagnosed late are troubling. Taking these issues into account along

CONTENTS

How did we get here? The history behind HIV exceptionalism

The evolution of HIV-testing

The role of screening for acute HIV infection

Where are we going? Towards routine HIV testing

Routine HIV screening

Barriers to implementation of routine HIV testing

Conclusions

Expert commentary

Five-year view

Financial disclosure

Key issues

References

Affiliations

[†]Author for correspondence
STD Prevention and Control
Services, San Francisco Department
of Public Health, 1360 Mission
Street, Suite #401, San Francisco,
CA 94103, USA
Tel.: +1 415 355 2000
Fax: +1 415 554 9636
jeff.klausner@sfdph.org

KEYWORDS:
acute HIV infection, HIV
exceptionalism, HIV testing,
routine HIV screening

with new advances in HIV diagnostic tests and the availability of life-saving treatment, the reality of the HIV epidemic today demands a shift in the HIV testing paradigm.

How did we get here? The history behind HIV exceptionalism

Highly political rather than public health-based HIV testing policies were an early response to the epidemic and were greatly shaped by the social context of the day. There was a time when 20% of the US population believed that people with AIDS were getting what they deserved and 30% believed seropositive individuals should be marked by tattoo [12]. The first HIV antibody test became available in 1985. However, fears regarding discrimination, stigma and the psychological effects of a diagnosis in the absence of effective treatment led many to question the utility of HIV testing.

As our understanding of the natural history and transmission of HIV infection increased, the question of how best to implement testing and screening engendered much debate and discussion. While public health officials recognized the role of HIV testing as a cornerstone of disease control, those prioritizing civil liberties and the privacy of people with HIV infection won the day. A brand of 'HIV exceptionalism' [13] was created in which detailed procedures for testing, including separate written consent and in-depth pre- and post-test counseling, were established and implemented across the country. In addition, HIV testing, according to the 1987 US Public Health Service guidelines, was to be prioritized only for those

deemed to be at high risk for infection or who practiced high-risk behaviors [14]. While the CDC has maintained the importance of risk-based screening and rescreening on an annual basis for high-risk individuals in their latest guidelines, the CDC has moved toward the endorsement of universal testing for the general adult population [2,14]. However, risk-based testing and not universal testing remains the norm in most of the USA.

The evolution of HIV testing

Today, many different HIV tests are available for general use. These tests include conventional (nonrapid), rapid, oral fluid or urine, and viral RNA or DNA tests. Within each of these categories the tests often use different substrates targeting either the antibodies against the virus or the virus itself. Each test also has a different 'window period', which refers to the time between infection and the test's ability to detect HIV (FIGURE 1).

Enzyme immunoassays (EIAs) were the first test developed for the diagnosis of HIV infection in 1985 [15]. Currently, four generations of EIAs exist, each one detecting a different antibody, group of antibodies or viral proteins and shortening the window period (FIGURE 1 & TABLE 1). Although highly sensitive in detecting HIV infection and the most recent assays detecting infected individuals before seroconversion, all reactive EIAs require confirmation. The sensitive/less-sensitive ('detuned') and BED (indicating HIV subtypes B, E and D) IgG capture assays can evaluate the duration of HIV infection:

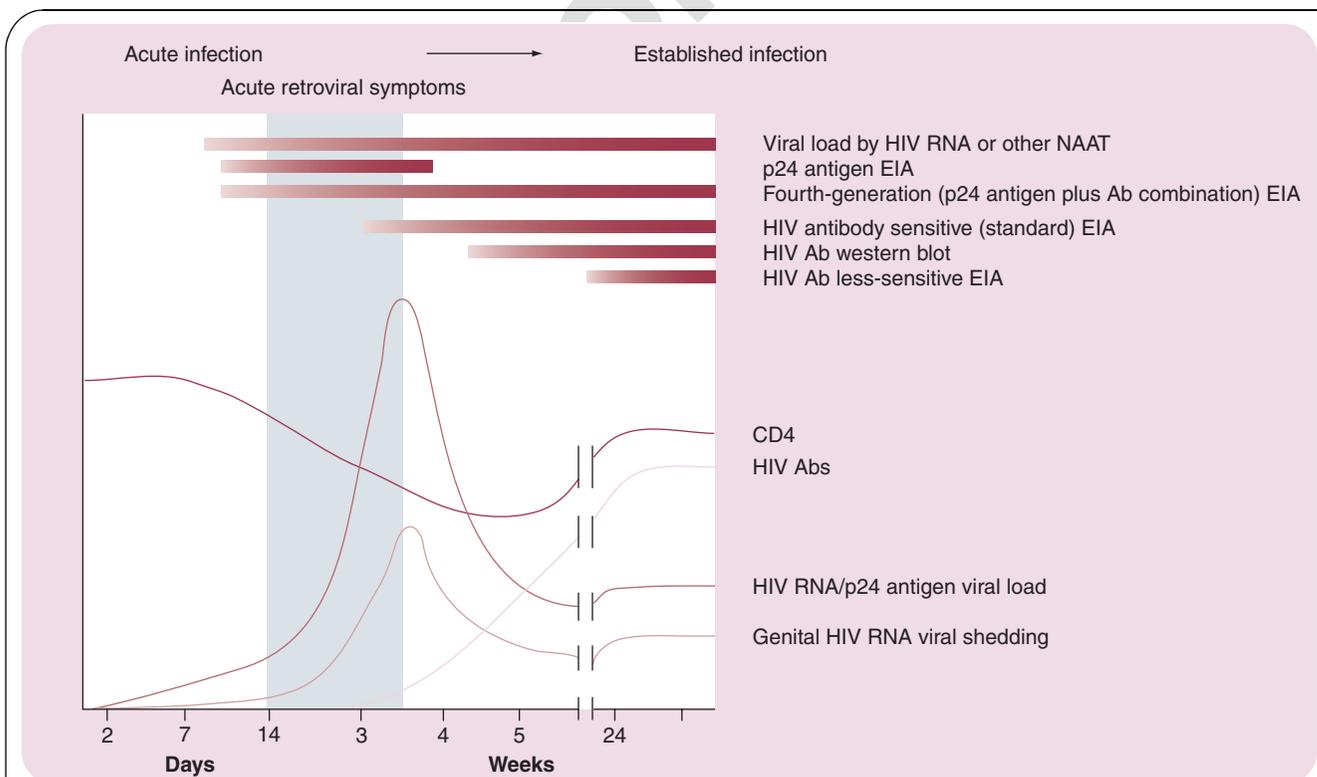


Figure 1. HIV technologies and their relationship with major events in the natural course of HIV infection.

Ab: Antibody; EIA: Enzyme immunoassay; NAAT: Nucleic acid amplification test.

Reproduced with permission from [52].

Table 1. Overview of HIV testing technologies.

Test type	Target and comments	Strengths	Weaknesses
First- and second-generation EIA	First generation is based on viral lysate. Second generation is based on synthetic peptides and recombinant proteins. Both detect IgG only	Excellent sensitivity and specificity when followed by confirmatory test; inexpensive, widely available	Window period of up to 6–12 weeks; requires up to 2 weeks for results due to testing logistics; requires a confirmatory test*
Third-generation EIA	Adds HIV Group O and HIV-2 antigen Detects IgG and IgM	Excellent sensitivity and specificity when followed by confirmatory test; decreases window period compared with first and second generation; detects more subtypes of HIV	Requires up to two weeks for results due to testing logistics; still has a substantial window period; requires a confirmatory test*
Fourth-generation EIA	Incorporates the use of p24 antigen detection	Excellent sensitivity and specificity when followed by confirmatory test; detection of IgM, IgG, and viral capsid protein leads to a reduced window period of 10–14 days; detects more subtypes of HIV; can be used, in conjunction with other generations of EIA testing, to determine chronic versus acute infection	Not yet cleared for use by the US FDA in the USA; requires up to 2 weeks for results due to testing logistics; transient antigenemia can make it hard to detect p24 antigen; requires a confirmatory test*
Rapid tests	EIAs that use synthetic structural proteins	Test results in 5–40 min; accuracy comparable to standard antibody tests; can be done with minimal training (e.g., at home); allows HIV testing to be moved out of healthcare settings (e.g., mobile clinics, health fairs)	Requires a confirmatory test*; window period comparable to second-generation EIA
Oral sample tests	Uses whole-cell purified and inactivated viral lysate and/or purified and inactivated HIV-1 antigen coated onto micro-ELISA wells.	Alternative to people who refuse/do not want a blood draw; accuracy comparable to serum antibody tests; can be done with minimal training (e.g., at home)	Availability not as widespread as EIA tests; requires a confirmatory test*
Urine tests	EIA and Western blot technologies using synthetic peptides and partially purified and inactivated HIV	Alternative to people who refuse/do not want a blood draw	Not widely available; requires a confirmatory test; still requires a confirmatory test*
Nucleic acid amplification tests	Currently, reverse-transcription PCR, nucleic acid sequence amplification and branched DNA are the technologies available	Highly sensitive with excellent specificity; able to diagnose HIV infection prior to antibody formation, in the traditional window period; can be used to diagnose patients with an indeterminate western blot; useful in following HIV disease progression; cost effective when pooled sample testing used	Not widely available for HIV diagnosis; expensive; best protocol for pooled sample testing not yet known; requires up to 2 weeks for results due to testing logistics
'Detuned' assays/BED IgG capture assays		Able to differentiate older/chronic HIV infections from newer/acute infection	Not widely available; not cleared FDA for clinical or routine public health use

*Confirmatory tests include Western blot, immunofluorescent assay, or Genprobe transcription-mediated amplification.
EIA: Enzyme immunoassay.

if HIV seroconversion was recent (within months to a year) or not. That categorization is based on the principle that older infections have higher antibody titers and higher antibody affinity for its substrate than more recent infections.

Rapid HIV tests can be read within 20 min and are designed so that people with minimal training can administer them. Although positive rapid HIV tests do require a confirmatory test, they could potentially bridge the gap between the 30% of Americans who get tested for HIV infection but do not return for their results [16]. Recently, an analysis of four

studies comparing the US FDA-cleared OraQuick Advance rapid HIV-1 test with standard testing methods, with western blot confirmatory test, showed a sensitivity of 99.7% and specificity of 99.9% with blood samples [17]. There is evidence to suggest that the inclusion of rapid HIV testing into traditional community-based HIV prevention programs may be more acceptable and increase the number of people tested [18].

There are also HIV tests that detect antibody to the virus in other specimens, such as oral secretions. The OraQuick Advance rapid HIV-1 test is reported to have very good sensitivity and

specificity with oral secretions, 99.1 and 99.6%, respectively [17]. Urine testing for HIV by EIA and HIV testing using finger stick specimens of dried whole blood on filter paper are also available. Altogether, these new technologies provide rapid, noninvasive, simple ways to test for HIV infection, enabling for community-based testing campaigns, point-of-care HIV testing and, potentially, even home-based testing.

Tests for the detection of viral RNA or DNA are available but expensive. To date, these tests are not routinely used for HIV diagnosis, rather they are used as quantitative tests to monitor the progression of HIV disease. However, increasingly, efforts to diagnose acute HIV infection are making use of nucleic acid tests by pooling specimens to reduce testing costs [19]. During the antibody-negative phase of early HIV infection, detection of amplified viral nucleic acids is possible. The sensitivity and specificity of nucleic acid amplification tests (NAATs) have been reported to be 94–98% and 99–99.9%, respectively [20,21].

The role of screening for acute HIV infection

Despite increasing evidence suggesting the role of acute HIV infection as a main driver of the epidemic, the inability to identify cases of acute HIV infection has limited the ability of public health officials to control the epidemic. Detection of acute HIV infection is complicated by the lack of consistent, specific, and easily recognizable clinical manifestations and the lack of detectable serum HIV antibodies. However, recent advances in testing, such as the use of NAATs, fourth-generation EIAs and detuned antibody testing, have made the detection of acute and early HIV infection a realistic undertaking.

Acute HIV infection, with its high levels of viremia, viral shedding and amplification, is a highly infectious state. Combined with the lack of awareness most newly HIV-infected individuals have regarding their infection status, individuals with acute HIV infection may contribute to the spread of nearly half of incident infections. Mathematical modeling of HIV transmission has shown that this hyperinfectious stage of acute HIV infection may have been responsible for the global spread of the virus [22]. Epidemiologic studies have borne out the conclusion that recent infection does increase the risk of HIV transmission to a sex partner [23–25]. Therefore, the ability to diagnose an acute HIV infection has great potential value from a public health standpoint. Identifying people with acute HIV infection would reduce the high rate of viral transmission in this hyper-infectious group. Additionally, it would allow public health officials to use time-tested outbreak control efforts, similar to those used in tuberculosis control programs, which focus on reducing ongoing transmission from the most contagious cases. That will only be possible if accurate and timely information on seroconversion and sexual or social networks where recent transmission has occurred are monitored linking HIV surveillance to HIV prevention.

One of the main concerns regarding the expansion of programs to detect acute HIV infection has been the cost. Using molecular testing, such as NAATs, is prohibitively expensive for screening on an individual level. However, the use of

pooled-sample screening protocols, which have become standard in some industries, can substantially reduce the costs of testing. The blood bank has used pooled-sample HIV nucleic acid screening since 1999 [26] and it has the public health potential to screen individuals for acute HIV infection. Currently, blood banks test all units individually for HIV infection by antibody testing. Aliquots of seronegative units are pooled into batches consisting of specimens from multiple units of blood. These batches are then tested using a NAAT. If the batch is negative, the testing is finished. All the original units are classified as negative for HIV infection. If the batch has a positive NAAT result then the units making up that batch are retested using individual specimens to determine the unit containing HIV [26]. Some public health agencies in the USA are successfully incorporating pooled NAATs into their HIV testing protocols. In San Francisco, routine screening for acute HIV infection using HIV nucleic acid testing resulted in an increase in HIV case detection of 8.8% at the municipal STD clinic [27]. In a recent study, Priddy *et al.* demonstrated that using only antibody testing in a high-risk urban population missed 6% of cases [28]. Although the absolute prevalence rates of acute HIV infection in these two studies were small, 0.3% and 0.18%, respectively, they support routine screening with pooled NAAT protocols in select populations.

Although highly successful, the implementation of screening programs for acute HIV infection is currently limited to a few publicly funded HIV testing sites and targeted to particular populations [20]. The principal limitation of efforts to detect patients with acute HIV infection remains its reliance on individuals to request HIV testing. Several studies have shown a high frequency of missed opportunities in diagnosing acute HIV infection in patients in hospital settings, emergency departments, urgent care clinics, and sexually transmitted disease (STD) clinics [29–33]. To have a true impact on the epidemic, screening for acute HIV infection should be expanded to and widely implemented in all sites where HIV testing occurs. HIV RNA screening should be a reflex test performed on all HIV antibody-negative specimens.

A particularly promising HIV testing protocol combines case identification and linkage to care using rapid HIV tests with the high sensitivity of pooled NAATs [34]. In our experience, combining rapid HIV antibody testing with pooled NAATs significantly raised the HIV case detection rate. At the San Francisco municipal STD clinic, select high-risk patients were offered rapid HIV testing. Those who tested antibody negative were tested for HIV RNA using a one stage pooling protocol of ten blood specimens. Adding HIV nucleic acid testing raised the HIV case detection rate by 19% [32]. This success suggests that the routine addition of a NAAT with every HIV antibody test may be the best test protocol.

An alternative testing strategy for the detection of cases of acute HIV infection would be to use the fourth-generation EIA *in lieu* of pooled nucleic acid testing. A recent study of patients attending STD clinics in Lilongwe, Malawi demonstrated the efficacy of using rapid HIV antibody testing and

p24 antigen testing compared with a NAAT to detect individuals with acute HIV infection [35]. Patients with acute HIV infection were detected among those who tested positive for HIV infection by the fourth-generation EIA and retesting them with an earlier (less sensitive) generation EIA test. If the early-generation EIA was negative then the person had a recent or acute HIV infection. Positive fourth-generation EIAs require confirmation by either NAAT or a neutralization assay. Unfortunately, however, a fourth-generation EIA is not currently cleared by the US FDA for marketing in the USA.

Where are we going? Toward routine HIV testing

Across the USA, there are vast differences in testing and counseling practices. As of 2004, 31 states required informed consent before HIV testing, although the method, written or verbal differed in each. A total of 23 states required pretest counseling and 40 states regulated which personnel could offer HIV testing, while only 29 regulated who could offer counseling [36]. The CDC's new recommendations, released in September 2006, are designed to lead HIV testing in the USA to a future where HIV testing will be a routine screening test available at all places where people access healthcare. The CDC recommends routine, opt-out screening for adult patients in all healthcare settings, annual screening/rescreening for HIV infection in high-risk populations and the elimination of any testing barriers, such as requirements for separate informed written consent for HIV testing [14].

The use of risk-based screening alone is an anachronism from the past and has failed to identify a substantial number of people who are HIV infected [37,38]. Chen *et al.* conducted a study of the utility of risk-based testing in a STI clinic. They found that testing persons based on traditional risk groups (e.g., MSM and intravenous drug users) resulted in the diagnosis of only 39% of HIV infections [37]. Klein *et al.* conducted a systematic review of medical encounters of patients before an eventual HIV diagnosis. They found that only 26% of people with an eventual HIV diagnosis had a documented sexual or injection risk behavior for HIV infection more than 1 year before diagnosis [38]. The cumbersome consent and counseling requirements for the patient-centered risk reduction approach reduced the ability of health professionals to test for HIV infection. Indeed, one of the biggest obstacles to the implementation of earlier CDC recommendations for routine HIV counseling and testing was that providers in busy healthcare settings often lacked the time and training to do risk assessment and in-depth counseling [39]. In a recent study, we demonstrated a significant increase in HIV-testing rates and HIV-case detection associated with a change in administrative policy. In May 2006, the San Francisco Department of Public Health medical care system, which includes the county hospital and over 15 primary care clinics, eliminated the requirement for separate written consent before HIV testing. Following this change in policy, the number of HIV tests performed increased steadily from 13.5 HIV tests per 1000 patient-visits in June 2006 to 17.9 HIV tests per 1000 patient-visits in

December 2006. Furthermore, the average number of positive tests per month increased from 20 to 31 after the change in policy [40].

The use of risk-based screening alone reinforces HIV-related stigma by separating HIV testing from routine medical care. Originally, stigma against those with HIV infection was a significant barrier to testing. While stigma and discrimination still do exist, the extent is currently much less than at the outset of the epidemic. Marginalized populations continue to bear a disproportionate burden of HIV diagnoses; however, antidiscrimination laws have been enacted at state and federal levels, including The American Disabilities Act of 1990 which banned discrimination on the basis of HIV or AIDS diagnosis at the federal level [41]. Today, the initial safeguards of confidentiality and civil liberty developed with regards to HIV infection in the late 1980s have turned into public health roadblocks. Routine HIV testing meets all the criteria for a useful screening test: it is a serious disease that can be diagnosed before symptoms develop and effectively treated to prevent complications. Detection of HIV infection is by a reliable, noninvasive and cost-effective test that can save years of life for those diagnosed early [42]. Cost-benefit analyses have shown that, even in relatively low-prevalence populations, screening for HIV is cost effective and on par with routine standard screening programs for other chronic diseases [37,43].

Routine HIV screening

A public health intervention

From a public health perspective, there is interest in using HIV testing as a means of disease control. The hypothesis that newly HIV-infected individuals will reduce their risk behavior is well supported in the literature. A recent meta-analysis by Marks *et al.* examined the results from 11 studies on high-risk sexual behavior and knowledge of HIV serostatus. They found that the incidence of unprotected anal or vaginal intercourse was 68% lower in HIV-infected individuals who were aware of their serostatus relative to those HIV-infected individuals unaware of their status [8]. Colfax *et al.* looked at sexual risk behavior and HIV transmission among homosexual men and other MSM. They found that receipt of a positive HIV test was associated with a reduction in high-risk sexual behavior, as defined by unprotected anal intercourse [44]. Among women, a study of female crack cocaine users showed that women who were aware of their HIV-positive status were less likely to engage in unprotected sex than women who were HIV negative [45]. Altogether, while the literature on HIV testing as a means of disease control fails to include a randomized clinical trial, the evidence in adults, both men and women, suggests that learning that one is HIV infected impacts behavior and can have substantial public health benefit.

However, for routine HIV testing to be an effective public health intervention, it needs to be widely available and used frequently. As mentioned earlier, one of the weaknesses of the current system of HIV testing is the reliance on patients to present to a testing site or medical facility. Going beyond the recent

CDC recommendations, one way to expand HIV screening would be to increase the offering of HIV testing in various institutional settings. Although serious consideration must be given to the implications of positive test results in some settings, requiring the offering of voluntary HIV testing in jails and prisons, for those obtaining public subsidies including health insurance and those entering drug treatment programs would be a step forward to achieve truly population-wide screening.

A clinical prevention tool

Routine HIV screening also has clinical impact as a prevention tool. Much research has documented the missed opportunities for HIV diagnosis in men and women [29,30,46]. The detection and diagnosis of HIV infection earlier and the reduction in the number of 'late testers' could prevent substantial morbidity and mortality resulting from advanced disease. Evidence supports that 12–43% of newly diagnosed HIV cases have CD4 T-cell counts of less than 200/ μ l [47]. Given that a person with HIV infection who seeks testing and treatment at a CD4 T-cell count of more than 350/ μ l has a 75% chance of living 8 years compared with 35–50% for those with lower CD4 T-cell counts, late diagnosis can be deadly [46]. The medical costs of treating an HIV-positive patient with a CD4 T-cell count of more than 350/ μ l for 1 year is US\$28,000 less than the costs associated with a person with a CD4 T-cell count of less than 50/ μ l [48]. Additionally, there is some evidence to suggest that HIV-positive patients with lower CD4 T-cell counts have poorer responses to antiretroviral therapy [45], underscoring the need to reduce missed opportunities in early HIV diagnosis.

Routine HIV testing also has clinical implications for the prognosis and treatment of acute HIV infection; it may be possible to alter the course of the illness with antiretroviral treatment in the acute phase of infection [49,50]. Although this is an area of active research without definitive answers, there is some evidence that treatments in the early stages of HIV infection might limit the population of latently infected cells [51]. These latently infected cells represent the main barrier to eradication of HIV in infected individuals today. Limiting viral replication would potentially have other beneficial effects, such as limiting viral diversification [52].

Not a new idea

Two areas in which routine screening have been implemented with enormous success are the prevention of maternal-to-child HIV transmission and the protection of the US blood supply. Following the discovery that zidovudine could markedly reduce vertical HIV transmission in 1995, integration of HIV screening with antenatal care was proposed [53]. Eventually routine, opt-out screening for pregnant women with a streamlining of pretest counseling and, in most states, the elimination of specific requirements for written consent were implemented. This type of routine screening has since proved much more effective than risk-based testing for identifying unsuspected maternal HIV infection and preventing vertical transmission [54,55].

Along with administration of antiretroviral drugs, it has reduced vertical transmission of HIV from a peak of 1650 perinatal HIV infections in 1991 to 144–236 in 2002 [56]. In the USA, blood banks' routine screening of blood donors for HIV infection, including the use of pooled RNA testing, has all but eliminated transfusion-associated HIV transmission [57].

However, implementation of routine HIV testing in the general population remains controversial. The largest point of contention is the proposed elimination of separate written informed consent. That has resulted in resistance from some civil liberty groups, including the American Civil Liberties Union and certain AIDS activists who believe it would lead to people being tested for HIV infection without their consent or knowledge. Concerns have also been raised regarding the potential high rates of false positive tests if nationwide screening and routine testing were to be implemented; however, the latest data show that, even in low-prevalence populations, the false positive rate is one in 250,000 [58]. Finally, some have questioned the cost-effectiveness and the anticipated impact on already overstretched healthcare systems.

Barriers to implementation of routine HIV testing

Apart from public support and controversy, logistical difficulties in implementing these new CDC recommendations do exist. The varied state laws in the USA that deal with HIV testing and counseling present a significant barrier as many of these laws mandate the exact opposite of the new CDC recommendations [59]. Additionally, if routine testing were implemented in all healthcare settings, as recommended by the new CDC guidelines, the increased volume of people undergoing testing has the potential to overwhelm current laboratory and medical care resources. To alleviate the stress that routine testing in medical care settings might impose, easy HIV testing without the current barriers of data collection and mandatory prevention counseling should be available in other publicly funded settings.

Many cities and states continue to use innovative measures to expand HIV testing outside of medical care settings. In San Francisco, climate-controlled tents have been used to provide HIV testing to residents in low-income neighborhoods [60]. Community-based testing in homeless shelters with rapid HIV antibody tests has also shown great promise [61]. Similar community-based testing initiatives have occurred in Massachusetts with testing sites in domestic violence shelters, local colleges, churches and youth groups [62]. These community-based testing efforts could be expanded further to include rapid-testing kiosks in malls, adult bookstores, bars, dance clubs, and restrooms. In this way, private, rapid and confidential testing could be achieved for people who cannot or do not access regular health services. Low-cost over-the-counter test kits or self home testing kits represent other opportunities to relieve the burden at traditional testing sites and expand HIV testing. To facilitate uptake of those alternative testing sites, the Internet could be used for promotion. For example, local public health department homepages could list the options for HIV testing

outside of health care facilities or even make self-completed test requisition forms available as is currently being done for syphilis testing [63,101]. With further creativity and efforts to undo dogmatic approaches to HIV testing, we can realize truly routine population-level screening.

Conclusions

The HIV epidemic has changed greatly over the last 25 years. The burden of HIV infections has shifted somewhat recently, spreading among some of the poorest and most marginalized of people. In the USA, we are missing tens of thousands of new HIV diagnoses each year. Those represent not only missed opportunities for individual treatment but failure to control the continued spread of the virus. The introduction of universal HIV testing has reduced the cases of vertical transmission and transfusion-associated transmission of HIV in a dramatic fashion; it is time to apply such tactics to sexually transmitted HIV infection.

Expert commentary

Current strategies to decrease the sexual transmission of HIV infection and increase the diagnosis and treatment of HIV infection depend on a risk-based testing approach that are cumbersome and outdated. While gains have been made in the fight against HIV infection with risk-based testing alone, far too many people remain either unaware of their infection or are diagnosed so late as to put their health seriously at risk. Where routine opt-out testing has been implemented, rates of transmission have dropped precipitously. It is rare to hear of HIV transmission from mother-to-child or associated with a blood transfusion in the USA today. The time has come to move forward with the integration of HIV testing into regular medical care with routine, opt-out screening in healthcare settings, as the new CDC guidelines recommend. Routine screening for

acute HIV infection with new testing modalities and the expansion of the offering of voluntary testing at nonhealthcare settings go beyond the CDC guidelines but are necessary steps. Together, this three-pronged approach to HIV testing will increase HIV testing, further decrease the stigma associated with testing, produce earlier HIV diagnosis and treatment and enhance the control of the epidemic.

Five-year view

Today, HIV testing practices vary greatly across the USA. Under increasing calls for change by medical and public health agencies, such as the CDC and the Institute of Medicine, HIV testing will evolve dramatically. Rather than the risk-based testing that most states and clinicians adhere to today, HIV testing will become a part of routine medical care over the next 5–10 years. This will be accomplished by the establishment of routine, opt-out HIV testing in medical care settings, similar to that which is offered to pregnant women in antenatal care today. The further expansion and simplification of testing in nontraditional testing sites, such as at home and in the community will also occur. That will not only alleviate the burden of testing in medical settings but also increase the uptake of testing among those not receiving medical care. Use of newer, more sensitive HIV testing modalities, such as NAATs, will allow clinicians to diagnose HIV infection earlier and enable public health officials to use real-time information to prevent nascent outbreaks and intervene in disease transmission networks with proven public health tactics.

Financial disclosure

This project was supported in part by the California HIV/AIDS Research Program (CHRP) CHO5-SMCHC-612 and the San Francisco Department of Public Health.

Key issues

- Despite great efforts aimed at increasing HIV testing and reducing the spread of disease, 25% of people with HIV are unaware of their infection and 40% of newly diagnosed HIV cases are diagnosed late in the course of disease.
- Current risk-based HIV testing strategies grew out of the discrimination and stigma directed at HIV patients during the start of the epidemic and do not maximally use public health tactics of disease control.
- A variety of HIV testing modalities are available today, many of which can be used to increase uptake and retention of HIV testing services and diagnose HIV disease at an earlier stage.
- Other areas in which routine HIV screening has been implemented, for example, pregnant women and the blood bank, have seen great successes in reducing HIV transmission.
- Routine HIV screening, as put forth in the 2006 US CDC guidelines, can be both a public health intervention and a clinical prevention tool.
- The varied HIV counseling and testing practices that exist in the USA today should be replaced by simple, routine, opt-out screening for adult patients in order to integrate HIV testing into routine healthcare.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1 CDC. Pneumocystis pneumonia – Los Angeles. *Morb. Mortal. Wkly Rep.* 30(21), 250–252 (1981).

2 CDC. Advancing HIV prevention: new strategies for a changing epidemic – United States, 2003. *Morb. Mortal. Wkly Rep.* 52(15), 329–332 (2003).

- 3 CDC. The global HIV/AIDS pandemic, 2006. *Morb. Mortal. Wkly Rep.* 55(31), 841–844 (2006).
- 4 CDC. Twenty five years of HIV/AIDS – United States 1981–2006. *Morb. Mortal. Wkly Rep.* 55(21), 585–589 (2006).
- 5 CDC. U.S. HIV and AIDS cases reported through December 2001. *HIV/AIDS Surveillance Report* 13(2), 1–44 (2001).
- 6 CDC. Trends in HIV/AIDS diagnoses – 33 States, 2001–2004. *Morb. Mortal. Wkly Rep.* 54(45), 1149–1153 (2005).
- 7 Glynn M, Rhodes P. Estimated HIV prevalence in the United States at the end of 2003 Presented at: *National HIV Prevention Conference*. Atlanta, GA, USA June 2005 (Abstract T1-B1101).
- 8 Marks G, Crepaz N, Senterfit JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J. Acquir. Immune Defic. Syndr.* 39(4), 446–453 (2005).
- **Large meta-analysis showing that knowing one's HIV status does reduce high-risk behavior and possibly reduce transmission.**
- 9 CDC. Late versus early testing of HIV-16 sites, United States, 2000–2003. *Morb. Mortal. Wkly Rep.* 52(25), 581–586 (2003).
- 10 Castilla J, Sobrino P, De La Fuente L, Noguer I, Guerra L, Parras F. Late diagnosis of HIV infection in the era of highly active antiretroviral therapy: consequences for AIDS incidence. *AIDS* 16(14), 1945–1951 (2002).
- 11 Schwarcz S, Hsu L, Dilly JW, Loeb L, Nelson K, Boyd S. Late diagnosis of HIV infection: trends, prevalence, and characteristics of persons whose HIV diagnosis occurred within 12 months of developing AIDS. *J. Acquir. Immune Defic. Syndr.* 43(4), 491–494 (2006).
- 12 Chesney MA, Smith AW. Critical delays in HIV testing and care: the potential role of stigma. *Am. Behav. Sci.* 42(7), 1158–1170 (1999).
- 13 Bayer R, Fairchild AL. Changing the paradigm for HIV testing – the end of exceptionalism. *N. Engl. J. Med.* 355(7), 647–649 (2006).
- **Excellent review of the historical and social context of HIV testing and rationale for change in the future.**
- 14 CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings. *MMWR Recomm. Rep.* 55(RR14), 1–17 (2006).
- **The most recent guidelines and recommendations from the US CDC regarding HIV testing in adults, adolescents and pregnant women, which forms the basis for this review.**
- 15 Zetola N, Klausner JD. HIV testing: an update. *MLO Med. Labs Obs.* 38(9), 58, 60–63 (2006).
- 16 Wright AA, Katz IT. Home testing for HIV. *N. Engl. J. Med.* 354(5), 437–440 (2006).
- 17 Delaney KP, Branson BM, Uniyal A *et al.* Performance of an oral fluid HIV-1/2 test: experience from our four CDC studies. *AIDS* 20(12), 1655–1660 (2006).
- 18 Speilberg F, Branson B, Goldbaum GM *et al.* Choosing HIV counseling and testing strategies for outreach settings. *J. Acquir. Immune Defic. Syndr.* 38(3), 348–355 (2005).
- 19 Sherlock M, Zetola NM, Klausner JD. Routine detection of acute HIV infection through RNA pooling: survey of current practice in the United States. *Sex. Transm. Dis.* 34(5), 314–316 (2007).
- 20 Pilcher CD, Fiscus SA, Nguyen TQ *et al.* Detection of acute infections during HIV testing in North Carolina. *N. Engl. J. Med.* 352(18), 1873–1883 (2005).
- 21 Yilmaz G. Diagnosis of HIV infection and laboratory monitoring of its therapy. *J. Clin. Vir.* 21(3), 187–196 (2001).
- 22 Koopman JS, Jacquez JA, Welch GW *et al.* The role of early HIV infection in the spread of HIV through populations. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 14(3), 249–258 (1997).
- 23 Leynaert B, Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. European study group on heterosexual transmission of HIV. *Am. J. Epidemiol.* 148(1), 88–96 (1998).
- 24 Nicolau JE, Benard G, Fonseca LA *et al.* HIV transmission to stable sexual partners of HIV infected Brazilian hemophiliacs. *Sao Paulo Med. J.* 114(3), 1186–1189 (1996).
- 25 Wawer MJ, Gray RH, Sewankambo NK *et al.* Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J. Infect. Dis.* 191(9), 1403–1409 (2005).
- 26 Stramer SL, Glynn SA, Kleinman SH *et al.* Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid amplification testing. *N. Engl. J. Med.* 351(8), 760–768 (2004).
- 27 Klausner JD, Grant RM, Kent CK. Detection of acute HIV infections. *N. Engl. J. Med.* 353(6), 631–633 (2005).
- **Shows that incorporation of nucleic acid amplification test (NAAT) testing significantly increases the case detection of HIV in San Francisco, CA, USA.**
- 28 Priddy FH, Pilcher CD, Moore RH *et al.* Detection of acute HIV infections in an urban HIV counseling and testing population in the United States. *J. Acquir. Immune Defic. Syndr.* 44(2), 196–202 (2007).
- 29 Daar ES, Little S, Pitt J *et al.* Diagnosis of primary HIV-1 infection. Los Angeles County primary HIV infection recruitment network. *Ann. Intern. Med.* 134(1), 25–29 (2001).
- 30 Weintrob AC, Giner J, Menezes P *et al.* Infrequent diagnosis of primary human immunodeficiency virus infection: missed opportunities in acute care settings. *Ann. Intern. Med.* 163(17), 2097–2100 (2003).
- 31 Patel P, Klausner JD, Bacon OM *et al.* Detection of acute HIV in high risk patients in California. *J. Acquir. Immune Defic. Syndr.* 42(1), 75–79 (2006).
- 32 Pincus JM, Crosby SS, Losina E, King ER, LaBelle C, Freedberg KA. Acute human immunodeficiency virus infection in patients presenting to an urban urgent care center. *Clin. Infect. Dis.* 37(12), 1699–1704 (2003).
- 33 Rosenberg ES, Caliendo AM, Walker BD. Acute HIV infection among patients tested for mononucleosis. *N. Engl. J. Med.* 340(12), 969 (1999).
- 34 Klausner J, Philip S, Ahrens K *et al.* Combined rapid and RNA testing improves case detection and potential prevention in a public STD clinic, San Francisco 2004–2006. Presented at: *14th Conference on Retrovirus and Opportunistic Infections*. Los Angeles, CA, USA, 25–28 February 2007.
- 35 Fiscus SA, Pilcher CD, Miller WC *et al.* Rapid, real time detection of acute HIV in patients in Africa. *J. Infect. Dis.* 195(3), 416–424 (2007).
- 36 Hodge JG. Advancing HIV Prevention initiative: a limited legal analysis of state HIV statutes: initial assessment for the Centers for Disease Control and Prevention, as of September 2004: the center for law and the public's health at Georgetown and John's Hopkins Universities. *AHP Report.* (2004).
- 37 Chen Z, Branson B, Ballenger A, Peterman TA. Risk assessment to improve targeting of HIV counseling and testing services for STD clinic patients. *Sex. Transm. Dis.* 25(10), 539–543 (1999).
- 38 Klein D, Hurley LB, Merrill D,

- Quesenberry CP Jr; Consortium for HIV/AIDS Interregional Research. Review of medical encounters in the 5 years before a diagnosis of HIV-1 infection: implications for early detection. *J. Acquir. Immune Defic. Syndr.* 32(2), 143–152 (2003).
- 39 Walensky RP, Weinstein MC, Kimmel AD *et al.* Routine human immunodeficiency virus testing: an economic evaluation of current guidelines. *Am. J. Med.* 118(3), 292–300 (2005).
- **Economic analysis that shows the cost-effectiveness of routine HIV testing in low-prevalence populations.**
- 40 Zetola NM, Klausner JD, Haller B, Nassos P, Katz MH. Association between rates of HIV testing and elimination of written consents in San Francisco. *JAMA* 297(10), 1061–1062 (2007).
- **Shows the increase in uptake of HIV testing after the elimination of the requirement of written consent in the San Francisco Department of Public Health (USA) medical care system.**
- 41 Gostin LO, Ward JW, Baker AC. National HIV case reporting for the United States: a defining moment in the history of the epidemic. *N. Engl. J. Med.* 337(16), 1162–1167 (1997).
- 42 Wilson JM, Jungner G. *Principles and Practice of Screening for Disease.* WHO, Geneva, Switzerland (1968).
- 43 Paltiel AD, Weinstein MC, Kimmel AD *et al.* Expanded screening for HIV in the United States – an analysis of cost-effectiveness. *N. Engl. J. Med.* 352(6), 586–595 (2005).
- 44 Colfax GN, Buchbinder SP, Cornelisse PG, Vittinghoff E, Mayer K, Celum C. Sexual risk behaviors and implication for secondary HIV transmission during and after HIV seroconversion. *AIDS* 16(11), 1529–1535 (2002).
- 45 Brewer TH, Zhao W, Metsch LR, Coltes A, Zenilman J. High risk behavior in women who use crack: knowledge of HIV serostatus and risk behavior. *Ann. Epidemiol.* 17(7), 533–539 (2007).
- 46 Liddicoat RV, Horton NJ, Urban R, Maier E, Christiansen D, Samet JH. Assessing missed opportunities for HIV testing in a medical setting. *J. Gen. Intern. Med.* 19(4), 349–356 (2004).
- 47 Chou R, Huffman, LH, Fu R, Smits AK, Korthuis PT; US Preventative Services Task Force. Screening for HIV: a review of the evidence for the US Preventative Service Task Force. *Ann. Intern. Med.* 143(1), 55–73 (2005).
- 48 [No author listed]. Nationwide effort targets earlier diagnosis and treatment for HIV. *Dis. Manag. Advis.* 7(11), 170–172, 161 (2001).
- 49 Smith DE, Walker BD, Cooper DA, Rosenberg ES, Kaldor JM. Is antiretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? *AIDS* 18(5), 709–718 (2004).
- 50 Chun TW, Justement JS, Moir S *et al.* Decay of the HIV reservoir in patients receiving antiretroviral therapy for extended periods: implications for eradication of virus. *J. Infect. Dis.* 195(12), 1762–1764 (2007).
- 51 Kassutto S, Rosenberg ES. Primary HIV type 1 infection. *Clin. Infect. Dis.* 38(10), 1447–1453 (2004).
- 52 Zetola NM, Pilcher CD. Diagnosis and management of acute HIV infection. *Infect. Dis. Clin. North Am.* 21(1), 19–48 (2007).
- 53 Conner EM, Sperling RS, Gelber R, *et al.* Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N. Engl. J. Med.* 331(18), 1173–1180 (1994).
- 54 Barbacci MB, Dalabetta GA, Repke JT *et al.* Humman immunodeficiency virus infection in women attending an inner-city prenatal clinic: ineffectiveness of targeted screening. *Sex. Transm. Dis.* 17(3), 122–126 (1990).
- 55 Lindsay MK, Adefris W, Peterson HB, Williams H, Johnson J, Klein L. Determinants of acceptance of routine voluntary human immunodeficiency virus testing in an inner-city prenatal population. *Obstet. Gynecol.* 78(4), 678–690 (1991).
- 56 CDC. Achievements in public health: Reduction in perinatal transmission of HIV infection – United States 1985–2005. *Morb. Mortal. Wkly Rep.* 55(21), 592–597 (2006).
- **Reviews the reduction of vertical transmission of HIV after introducing opt-out routine screening among pregnant women accessing antenatal care.**
- 57 Dodd RY, Notari EP, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion* 42(8), 975–979 (2002).
- 58 Wynia MK. Routine screening: informed consent, stigma, and the waning of HIV exceptionalism. *Am. J. Bioeth.* 6(4), 5–8 (2006).
- 59 [No author listed]. California, Maine laws out of sync with CDC over routine HIV testing. *AIDS Policy Law* 22(2), 1, 4 (2007).
- 60 [No author listed]. Have tents, will travel in San Francisco. Testing facilities travel to clients. *AIDS Alert* 20(2), 21–22 (2005).
- 61 Butcher JB, Thomas KM, Guzman D, Riley E, Dela Cruz N, Bangsberg D. Community based rapid testing in homeless and marginally housed adults in San Francisco. *HIV Med.* 8(1), 28–31 (2007).
- 62 [No author listed]. Massachusetts project cuts a wide swath of care. Nontraditional testing sites is main focus. *AIDS Alert* 20(2), 18–19 (2005).
- 63 Levine DK, Scott KC, Klausner JD. Online syphilis testing – confidential and convenient. *Sex. Transm. Dis.* 32(2), 139–141 (2005).

Website

- 101 San Francisco City Clinic. Syphilis testing www.stdtest.org

Affiliations

- Rachel Smith, BA
School of Medicine, University of California, San Francisco, CA, USA
Tel.: +1 415 355 2000
Fax: +1 415 554 9636
rachel.smith@ucsf.edu
- Nicola M Zetola, MD
Division of Infectious Diseases, University of California, San Francisco, CA, USA
Tel.: +1 415 355 2000
Fax: +1 415 554 9636
nicola.zetola@sfdph.org
- Jeffrey D Klausner, MD, MPH
Director, STD Prevention and Control Services, San Francisco Department of Public Health, 1360 Mission Street, Suite #401, San Francisco, CA 94103, USA
Tel.: +1 415 355 2000
Fax: +1 415 554 9636
jeff.klausner@sfdph.org