

RESEARCH INITIATIVE

Treatment Action!

Three Biggest HIV Problems in the United States:

Late Testing, Late Care,
Early Dropout **by Mark Mascolini**

INTERVIEWS WITH:

Bernard M. Branson, MD

Opt-out HIV testing: key questions on cost and implementation

Michael J. Mugavero, MD

Testing, linking, retaining:
An HIV clinician's perspective



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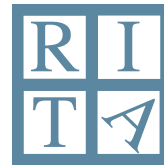
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Dear reader,

Thirty years ago this month, the Centers for Disease Control (CDC) issued its first report on what would come to be known as Acquired Immune Deficiency Syndrome. (The CDC described the cases of “five young men, all active homosexuals” who were suffering from a rare pneumonia.) Since then, advances in the treatment of HIV/AIDS have marked one of the most striking achievements of contemporary medicine. In only three decades, a diagnosis of HIV infection has gone from being a near-universal death sentence to the start of a chronic but survivable illness.

At The Center for AIDS, we tell clients that HIV disease is life altering but not life ending. But this observation comes with caveats. It applies to those who 1) get diagnosed, 2) enter care, 3) stay in care, and 4) adhere to therapy and suppress their viral load to below the limits of detection. Of the 1.1 million HIV-infected people in the United States, a distressingly low number of them complete all four steps. In fact, according to one study, fewer than 1 in 5 has an undetectable viral load.

In this issue of *RITA!*, editor Mark Mascolini explores what are now arguably the biggest HIV problems in the United States: late testing -- 21% of people infected with the virus don't know it; late care -- 20% of people infected with the virus know it but aren't in care; and early drop out -- 19% of people infected with the virus were in care but left.

In other words, roughly 60% of people who need care for HIV disease either don't know it or aren't getting care. This is a problem not just for these individuals, many of whom will go on to suffer needlessly, but also for the public health. Every year, the United States sees 56,000 new HIV infections; since treatment dramatically reduces transmission of the virus, the number of new infections could be cut sharply if more people living with the virus knew their serostatus and received treatment for their infection.

With this issue of *RITA!*, we hope to advance discussion about ways of achieving those goals.

Until there's a cure,

Paul Simmons, BSN, RN, ACRN
Executive Director



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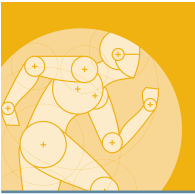
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Late HIV diagnosis: predictors, costs, consequences, and solutions

By Mark Mascolini

More than a million people in the United States have HIV infection, and fewer than 1 in 5 has an undetectable viral load.¹ That eye-popping estimate—based on a synthesis of recently published data—explains why HIV incidence stands at a staggering 56,000 yearly in the United States, and has since the turn of the millennium.²

You don't have to look far for the reasons behind these galling tallies: A perdurably high proportion of HIV-positive people remains untested; those who test positive sometimes never see the inside of an HIV clinic; and those who enter care drift away in waves. This triple threat to steady treatment—late diagnosis, sluggish linkage to care, and fleeting retention—conspire to keep the collective viral load so high that further HIV transmission is a foregone conclusion.

Researchers in Denver and Atlanta¹ started their analysis with the CDC estimate that 1.1 million

US residents have HIV infection and that 21% don't know it. From there, these arithmeticians cited published data to estimate that 75% of newly diagnosed people enter care within 6 to 12 months, while 80% to 90% get care within 3 to 5 years. Among people diagnosed with HIV, half do not stay in regular care. While 80% of HIV-positive people in care should start antiretroviral therapy (at the old 350 cells/mm³ threshold), 25% of that group do not begin treatment.

Figure 1 details the dwindling ratios of HIV-positive people who get diagnosed, enter care, stay in care, get treated, adhere to treatment, and reach an undetectable viral load. The bottom line reads like this: 209,773 HIV-positive people adhere to antiretroviral therapy and have no measurable virus in blood; that number represents 60% of all those who need antiretroviral therapy and 19% of the 1.1 million with HIV.

Limited HIV diagnosis, linkage to care, and retention in care in the US

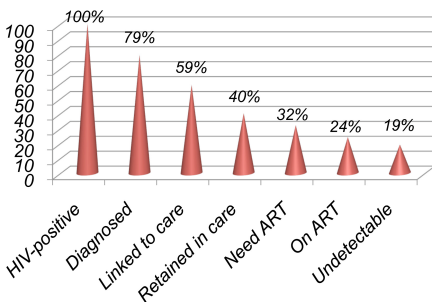


Figure 1. Of an estimated 1.1 million HIV-positive people in the United States, 79% are diagnosed, 59% enter care, and 40% stay in care, according to analysis of recently published studies.¹ Of those retained in care, 80% need antiretroviral therapy (ART) (32% of 1.1 million), 75% begin treatment (24% of 1.1 million), and 60% adhere to treatment and reach an undetectable viral load (19% of 1.1 million).

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Next the researchers used a simple model to project how much the proportion of people with an undetectable viral load would climb if 90% of infected people got diagnosed, 90% entered care, 90% started antiretrovirals, and 90% notched a viral load below 50 copies/mL. When the investigators considered these parameters one by one, none did much to improve the undetectable rate. When they combined all four parameters, the proportion of HIV-positive US residents with an undetectable viral load jumped from 19% to 66%.

This review and the one starting on page 37 analyze recent research (most from the past 5 years) addressing three facets of this problem—late HIV diagnosis, delayed entry to care, and dropping out of care. For each problem, the review considers epidemiology, predictors, clinical consequences, and potential remedies. Interviews with Bernard Branson from the CDC and Michael Mugavero from the University of Alabama at Birmingham offer additional insights on these issues from policy-making and clinical points of view.

CDC says test everyone (almost)

As recommended CD4-count thresholds for starting therapy climb, definitions of late presentation or late HIV diagnosis also evolve. In 2011 a European consensus group proposed defining late presentation as coming to care with a CD4 count under 350 cells/mm³, while they defined “presentation with advanced HIV disease” as seeking care with a CD4 count under 200 cells/mm³.³ After analyzing 15,774 United Kingdom residents with HIV, the UK Collaborative HIV Cohort (UK CHIC) formulated essentially the same definition.⁴

An estimated 32% of Americans diagnosed with HIV in 2008 had AIDS within 12 months.⁸

To limit delayed HIV diagnosis and entry to care, in 2006 the Centers for Disease Control and Prevention (CDC) proffered a radical shift in HIV testing strategy for adolescents and adults (including pregnant women) in the United States.⁵ CDC experts advised health professionals to offer routine opt-out testing for everyone from 13 to 64—regardless of perceived HIV risk—whenever they seek care at a medical office or hospital, unless research shows that prevalence of undiagnosed HIV infection in the area lies below 0.1%. Opt-out testing means telling a person an HIV assay will be part of their routine bloodwork unless they specifically decline HIV testing. The CDC suggested pretest counseling and separate consent for HIV testing could be skipped. Repeat HIV testing is left to the provider’s discretion, based on perceived HIV risk. The CDC recommended at least annual testing for high-risk groups. The US Preventive Services Task Force outlines the following HIV risk factors:⁶

- Men who have had sex with other men since 1975
- Men and women who have unprotected sex with multiple partners
- Past or present injection drug users (IDUs)
- Men and women who exchange sex for money or drugs or have sex partners who do
- People whose past or present sex partners are HIV positive, bisexual, or IDUs
- People being treated for sexually transmitted diseases
- People who had a blood transfusion between 1978 and 1985
- People who request an HIV test

The CDC adds another high-risk category: anyone—gay or straight—“who themselves or whose sex partners have had more than one sex partner since their most recent HIV test.”⁵

Because people who know they have HIV may be more likely to avoid risky sex, the CDC argues, knowledge of HIV status “in unaware persons” might reduce new HIV infections by 30%.⁷ And of course knowing one’s HIV status is the first step to care. Although plenty of people disagree with the CDC strategy (see “Universal opt-out testing: pros and cons” below), no one doubts the pernicious impact of late HIV diagnosis on individual and public health. And as detailed in the next section, CDC data suggest the revised testing guidance has already begun to turn the tide.

Late HIV diagnosis: numbing numbers

HIV infects about 1 million people in the United States.⁸ For years the CDC reckoned that 40,000 more US residents got infected every year, but in 2008 (using a more precise estimating method) they bumped that number to 56,000 yearly—dating back to the year 2000.² An estimated 32% of Americans diagnosed with HIV in 2008 had AIDS within 12 months.⁸

Using that same definition of late diagnosis, the CDC tallied more dire data from 33 US states and Canada from 1996 through 2005, estimating a 54% late-diagnosis rate in the United States and a 64% rate in Canada.⁹ In the United States, proportions of people with a late HIV diagnosis were no higher among blacks (53%) or Hispanics (58%) than whites (54%). By 2011, however, in 33 states the CDC discerned a possible dip in late diagnoses that seemed to start in 2005.¹⁰ In these 33 states, the late-diagnosis rate held steady at 37% from 2001 to 2004, then slipped to 32.3% in 2007.

In a US-Canadian cohort of 44,491 people with HIV, CD4 count at diagnosis edged up by an average 6 cells/mm³ yearly from 1997 through 2007.¹¹ But median initial CD4 count reached only 317 cells/mm³ in 2007, well below the 350-cell antiretroviral start signal at the time. Among people older than 50, median initial CD4 count rose from 203 to only 266 cells/mm³ by 2007.¹² **Table 1** (page 8) summarizes these and other studies of CD4 count trends at HIV diagnosis.¹¹⁻¹⁷

Reports from Europe tell similar stories. In an 11-country European survey in 2009, about half of people with newly diagnosed HIV had a CD4 count under 350 cells/mm³.¹⁶ The rate was 50% or more in Denmark, France, Slovenia, Spain, and the United Kingdom. A study in England, Wales, and Northern Ireland found higher rates of late HIV presentation for care (under 350 cells/mm³ within 91 days of diagnosis) in people 50 and older (48% versus 33% in younger adults), and older late presenters had a 2.4 times higher risk of dying than younger late presenters within a year of diagnosis.¹⁷

The US-Canadian, Swiss, and British Isles studies underline the high risk of late presentation in older adults.^{12,15,17} These findings probably partly reflect low suspicion of HIV risk in older people and thus delayed testing. The North American study also found that the proportion of people 50 or older when first seeking HIV care rose from 1997 to 2007.¹² These results are particularly troubling because older people have a blunted CD4 response to antiretroviral therapy compared with younger people, even though older people tend to be better virologic responders. These investigators called for “targeted renewed prevention and testing strategies . . . in all age groups, including those 50-years-old and older.”¹²

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Table 1-A. Recent trends in CD4 count at HIV diagnosis or presentation to care

First author	Country	Number of participants	Years	Key findings
Althoff ¹¹	United States and Canada (NA-ACCORD cohort)	44,491	1997-2007	<p>Median CD4 count at presentation rose from 256 in 1997 to 317 in 2007.</p> <p>Fewer than half of cohort members, 46%, had a CD4 count above 350 at presentation in 2007.</p>
Althoff ¹²	United States and Canada (NA-ACCORD cohort)	44,491	1997-2007	<p>Older people had a lower CD4 count at presentation than younger people throughout the study period.</p> <p>Median CD4 count at presentation in 2007 was 266 in people 50 and older and 336 in younger adults.</p>
Keruly ¹³	United States (Baltimore)	3348	1990-2006	<p>Median CD4 count at presentation fell from 371 in 1990-1994 to 276 in 2003-2006.</p> <p>Male gender, black race, and older age were tied to a lower CD4 count at presentation.</p>
Gandhi ¹⁴	United States (Veterans Affairs Centers)	4368	1998-2002	<p>Half (51%) presented for care with a CD4 count below 200.</p>
Wolbers ¹⁵	Switzerland (Swiss HIV Cohort Study)	1915	1998-2007	<p>Overall median initial CD4 count was 331.</p> <p>Older age and nonwhite race raised the risk of a low CD4 count at presentation.</p> <p>Every 10 years of age lowered initial CD4 count by an estimated 63 cells/mm³.</p>

Table 1-B. Recent trends in CD4 count at HIV diagnosis or presentation to care

First author	Country	Number of participants	Years	Key findings
LikataVICIUS ¹⁶	Cyprus, Czech Republic, Denmark, France, Luxembourg, Netherlands, Romania, Slovakia, Slovenia, Spain, UK	10,167	2009	<p>In all but one country (Luxembourg, 24%), the proportion of people with a CD4 count below 350 at diagnosis stood above 40%.</p> <p>Rates of sub-350 counts at HIV diagnosis were 50% or higher in Denmark, France, Slovenia, Spain, and the UK.</p> <p>More than 60% of heterosexually infected people in the Czech Republic, the Netherlands, Slovakia, and the UK got diagnosed with a CD4 count under 350.</p>
Smith ¹⁷	England, Wales, Northern Ireland	8255 older adults	2007	<p>Almost half of people 50 and older (48%) had a late presentation for HIV care, defined as a CD4 count under 350 within 90 days of diagnosis, compared with 33% of younger adults.</p> <p>Older adults with late presentation were 2.4 times more likely to die within a year of diagnosis than younger adults with late presentation.</p>

Harbingers of belated diagnosis or presentation

Several studies published after 2005 in the United States, France, and Spain weighed factors that account for late HIV diagnosis or delayed entry to care (**Table 2**).¹⁸⁻²⁶ Older age proved the most consistent predictor of late diagnosis, although work in San Francisco found that people younger than 30 ran a higher risk of late HIV diagnosis than older people.¹⁸ This study involved

2139 people at least 13 years old diagnosed with AIDS from 2001 through 2005 and reported to the San Francisco Department of Public Health; 830 of them (39%) got their AIDS diagnosis within 1 year of their positive HIV test.

Compared with 30-to-39-year-olds, people younger than 30 had a doubled risk of late diagnosis (adjusted odds ratio [AOR] 1.99, 95% confidence interval [CI] 1.4 to 2.8).¹⁸ Late diagnosis

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risk did not differ between the 30-to-39 group and people 40 to 49 or people 50 and older. The researchers suggested the higher risk in younger people reflects their relative lack of awareness about HIV. They did not report how many of these young people were born outside the United States or infected heterosexually, two factors that also emerged as independent predictors of late diagnosis in this study (see below).

In contrast, three large studies in France,²³⁻²⁵ one in Spain,²⁶ and one in North Carolina²⁰ linked older age to delayed HIV diagnosis. The largest of these studies, involving 18,721 adults who enrolled in the French Hospital Database on HIV from 1997 through 2002, determined that age

over 30 doubled or tripled the risk of late access to care (depending on age range) compared with age under 30 (**Figure 2**).²³ The 30-to-40-year-old group had almost a doubled risk of delayed care (OR 1.89, 95% CI 1.74 to 2.06), while people 50 to 60 had a tripled risk (OR 3.05, 95% CI 2.69 to 3.46). One third of this big cohort—6687 people or 36%—had delayed access to care, defined as a CD4 count under 200 cells/mm³ or an AIDS diagnosis upon enrollment in the cohort. The French investigators underlined the gravity of late presentation to care among people older than 50, including a higher risk of clinical progression and comorbidities and a slower CD4 response to antiretrovirals.

Risk of late HIV diagnosis with older age

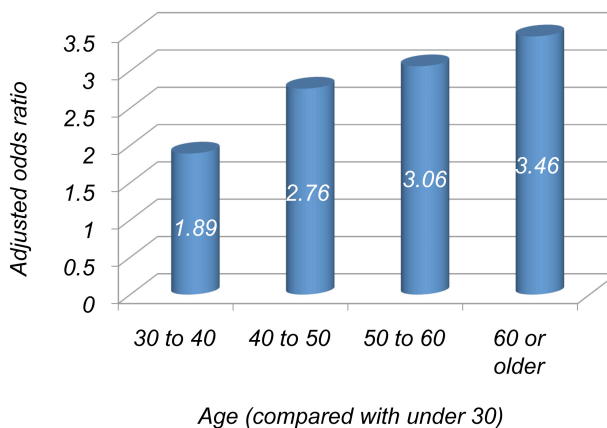


Figure 2. An 18,721-person analysis of the French Hospital Database on HIV determined that age over 30 independently raised the risk of having a CD4 count under 200 cells/mm³ or an AIDS diagnosis upon enrollment in the cohort.²³ Adjusted odds ratios (and 95% CI) for each age bracket were 1.89 (1.74 to 2.06), 2.76 (2.53 to 3.07), 3.06 (2.69 to 3.46), and 3.46 (2.91 to 4.12).

A six-center French study of 4516 people diagnosed with HIV from 1996 through June 2005 rated 1718 of them (38%) as “late testers,” defined as having a CD4 count under 200 cells/mm³ or an AIDS diagnosis in the year of their positive HIV test.²⁴ Again, late testing proved more prevalent in people over 30 than in younger adults. A third French study of 1077 people diagnosed with HIV since 1996 and enrolled in a nationally representative sample defined late testers the same way.²⁵ The investigators identified 384 late testers (36%). Compared with people younger than 25, every 5-year older age group had an independently higher risk of late HIV testing. People 40 and older (the oldest group) ran more than a 5 times higher risk of late testing (AOR 5.59, 95% CI 1.50 to 20.81).

A Spanish study involving 2564 people starting antiretroviral therapy from 2004 through 2006 reckoned that the risk of delayed HIV diagnosis rose linearly with age in men over 30, but an age effect was not seen in women.²⁶

At the Duke University HIV clinic in North Carolina, 55 of 113 people (49%) diagnosed with HIV between October 2002 and August 2004 had a CD4 count below 200 cells/mm³.²⁰ Age averaged 36 years and ranged from 17 to 61. Seventy-one of these people (63%) were black or Hispanic, and 31 (27%) were women. Every 10 years of age raised the risk of a sub-200 CD4 count at diagnosis 72% (AOR 1.72, 95% CI 1.12 to 2.64, *P* = 0.01). Forty people (35%) got diagnosed with HIV while admitted to the hospital. Every 10 years of age upped the risk of in-hospital diagnosis 79% (AOR 1.79, 95% CI 1.07 to 3.12, *P* = 0.03). Women had almost a 7 times higher risk of in-hospital diagnosis than men (AOR 6.74, 95% CI 2.08 to 21.81, *P* = 0.001), but the researchers did not have information on why these women were in the hospital. These clinicians believe “testing based on perceived risk of HIV infection, rather than broader screening approaches, likely contributes to the problem” of late diagnosis. (See the interview with Michael Mugavero in this issue for discussion of these findings.)

Table 2. Predictors of late HIV diagnosis or presentation to care

First author	Location	Number of late presenters	Risk factors for late diagnosis or presentation
Schwarzc ¹⁸	San Francisco	2139 adults and adolescents diagnosed with HIV and reported to the San Francisco Department of Public Health	Age younger than 30 Heterosexuals No reported HIV risk Private insurance No insurance Born outside US Opportunistic infection as initial AIDS diagnosis
Levy ¹⁹	Northern California	391 people attending a public AIDS clinic	Born outside US
Mugavero ²⁰	North Carolina	113 people attending a university HIV clinic	Older age Female gender

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Table 2 continued. Predictors of late HIV diagnosis or presentation to care

First author	Location	Number of late presenters	Risk factors for late diagnosis or presentation
Weis ²¹	South Carolina	4137 adults	Rural versus urban residence
Nelson ²²	Washington state	39 gay men recruited at HIV testing sites	Black race Gay disclosure to under 50% Only 1 sex partner in last 6 months
Lanoy ²³	France	18,721 adults in the French Hospital Database on HIV	Age over 30 versus under 30 Migrant women* Migrant men* Nonmigrant men* HIV transmission other than gay sex
Delpierre ²⁴	France	4516 adults	Heterosexual men vs gay men or heterosexual women Age over 30 years <i>Among heterosexual men:</i> Living in a couple with children <i>Among gay men:</i> Unemployment
Delpierre ²⁵	France	1077 adults in nationally representative cohort	Older age Heterosexual men Migrants <i>Among nonmigrants:</i> In long-term relationship, with children <i>Among migrants:</i> No recent steady partner Diagnosed during first year in France
Sobrino-Vegas ²⁶	Spain	2564 adults in 19 hospital clinics	Low education level Heterosexual vs gay transmission Drug injection vs gay transmission Age over 30 in men

*Compared with nonmigrant women.

Studies in France^{23,25} and the United States^{18,19} pinpointed nonnative birth as a predictor of late HIV diagnosis. Both US studies come from California, which has a large migrant population from Mexico and Central America. The 2139-person San Francisco Department of Public Health study included 402 people (19%) classified as Latino, 180 of whom (45%) had AIDS within 1 year of their HIV diagnosis.¹⁸ There were 301 people (14%) born outside the United States, 168 of whom (56%) had a late diagnosis. Birth outside the United States independently raised the risk of late diagnosis 64% (AOR 1.64, 95% CI 1.2, 2.2).

A study in the northern California country of San Mateo focused on 391 people attending a publicly funded HIV clinic from 2000 through 2002.¹⁹ Ninety-four study participants (24%) were born outside the United States. Foreign-born people were significantly more likely to have an opportunistic infection at HIV diagnosis (30% versus 17%, $P = 0.009$). Birth outside the United States emerged as the only independent predictor of opportunistic infection at HIV diagnosis, tripling the risk (AOR 2.98, 95% CI 1.21 to 7.38). These researchers observed that “migration results in increased sexual mixing of different groups, altered sex ratios of young adults (ratio of men to women) and social disruption that may discourage long term stable partnering patterns.”

The third late-diagnosis predictor identified in several studies is infection during heterosexual sex or by injecting drugs rather than during sex between men. Compared with transmission during sex between men, heterosexual transmission independently inflated the risk of late HIV diagnosis in the three French studies,²³⁻²⁵ a Spanish study,²⁶ and the San Francisco study.¹⁸ The 18,721-person French analysis determined that

injection drug use (versus sex between men) hoisted the risk of delayed HIV care 75%.²³ A study of 2564 people attending 19 hospital clinics in Spain from 2004 through 2006 found a doubled risk of delayed diagnosis in injection drug users compared with gay men.²⁶ In the San Francisco study, heterosexual HIV transmission versus male-to-male transmission nearly doubled the risk of late diagnosis (AOR 1.88, 95% CI 1.1 to 3.1).¹⁸ These findings clearly reflect heightened awareness of HIV among gay men.

Other independent predictors of late HIV diagnosis in US studies were private insurance or no insurance (versus public insurance),¹⁸ “no reported HIV risk,”¹⁸ and (in a study focusing on gay men) black race, gay disclosure to fewer than half of family and friends, and having only 1 sex partner in the past 6 months.²²

Together these findings bolster the CDC’s contention that people without classic HIV risk factors should be screened for infection. People who do not suspect they may pick up HIV during sex (older adults, heterosexuals) and people with limited access to medical care (migrants, rural residents) may be particularly vulnerable to complacency about HIV risk. US clinicians who conducted the North Carolina study recommended “routine rather than risk-based HIV testing . . . because high-risk behaviors are frequently not identified in primary care encounters.”²⁰

How much does late diagnosis cost—and who pays?

Studies analyzing the financial impact of late diagnosis consistently show that HIV care costs more when people come to the clinic (or hospital) with more advanced infection. But recent work also raises two important questions about more aggressive HIV screening in the United States:

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Does the healthcare system have the capacity to treat a big influx of newly diagnosed people? And where will the money for more testing—and treating—come from?

A study of 8348 newly diagnosed people at 10 US clinics in the HIV Research Network found that those diagnosed with a CD4 count under 200 cells/mm³ had higher direct costs for care than people diagnosed with more than 500 cells/mm³—and those higher costs persisted throughout the 2000-to-2007 study period.²⁷ Cumulative costs for late presenters versus early presenters were \$37,104 versus \$9829 in the first year of care, \$92,213 versus \$30,598 in the fifth year of care, and \$135,827 versus \$86,721 in the seventh year.

A Canadian study used the same CD4 cutoff for late presenters (below 200 cells/mm³) but a stricter threshold for early presenters (above 200 cells/mm³).²⁸ Of the 241 patients analyzed, 39% came to care with a sub-200 CD4 count. Direct costs in the first year of care totaled \$18,448 for late presenters and \$8455 for early presenters. Further statistical analysis showed that differences in patient traits did not explain the big cost contrast. Hospital costs accounted for the lion's share of the cost difference. A recent analysis by these same investigators used 350 cells/mm³ as the early-late threshold in people diagnosed from April 1998 through April 2003.²⁹ The disparity in direct costs during the first year of care (Canadian \$19,917 versus \$7840) remained substantial in the fifth year of care (Canadian \$15,663 versus \$8883).

Not all cost analyses concur that universal opt-out testing is a better deal than risk-based testing.

Cost-effectiveness studies—though hard to interpret for people unversed in modeling mazes—build the case for routine general-population HIV screening, at least on a one-time basis. A 2006 study by US researchers linked simulation models of various screening approaches to published reports of HIV transmission risk, with and without antiretroviral therapy.³⁰ The study population consisted of people with low to moderate HIV prevalence (0.05% to 1.0%) and annual HIV incidence (0.0084% to 0.12%). When the investigators figured that antiretroviral therapy has a moderately favorable impact on HIV transmission, cost-effectiveness ratios remained below \$50,000 per quality-adjusted life year for one-time screening with HIV prevalence as low as 0.20% and for screening every 5 years with prevalence as low as 0.45%.

A more recent US modeling probe weighed the impact of expanded HIV screening with or without antiretroviral therapy on new infections and cost per quality-adjusted life year in both a high-risk population (injection drug users and gay men) and a low-risk 15-to-64-year-old population.³¹ If people reduce sexual activity 20% after screening (a big if, suggest some studies discussed in the next section), one-time HIV screening of low-risk people plus annual screening of high-risk people could prevent 6.7% of a projected 1.23 million new infections and cost only \$22,382 per quality-adjusted life-year gained. Starting antiretrovirals when the CD4 count lies above 350 cells/mm³ would prevent 20% to 28% of projected new infections.

French modelers compared current risk-based HIV screening with universal routine screening in both the general adult population and high-risk subpopulations.³² Assuming undiagnosed HIV prevalence at 0.10% and annual HIV incidence at 0.01%, the model calculated one-time screening of the general population (versus current practice) increased quality-adjusted life months by only 0.01 (about 7 hours) while boosting costs by €50 (\$70) per person for a cost-effectiveness ratio of €57,400 (\$80,995). More frequent screening increased quality-adjusted life months, costs, and cost-effectiveness ratio. Still, the investigators believe one-time HIV screening of the general population compares favorably in cost-effectiveness when sized up against other screening interventions recommended in Western Europe.

Not all cost analyses concur that universal opt-out testing is a better deal than risk-based testing. Taking a payer's perspective and limiting the analysis to a single year, David Holtgrave of the Johns Hopkins Bloomberg School of Public Health figured that targeted testing would diagnose more HIV cases than opt-out testing (188,170 versus 56,940) if HIV prevalence stands at 1%.³³ Targeted testing would also prevent more HIV infections (14,553 versus 3644) at a lower gross cost per infection averted (\$56,383 versus \$237,149). Even when HIV prevalence stands as low as 0.3%, Holtgrave calculated that targeted testing performs better than opt-out testing in several outcome variables.

Responding to Holtgrave's analysis, CDC experts argued that "the scenarios upon which the analysis is based are implausible" (click on the Comments tab after opening the Holtgrave article in

the link provided in the references.³³) The CDC also observed that Holtgrave's analysis does not consider whether the alternatives to wide opt-out testing "are equally feasible or equally acceptable to patients and providers." (For details, see the interview with the CDC's Bernard Branson in this issue of *RITA!*)

Regardless of who's right about the cost-effectiveness of opt-out screening, it's worth remembering what cost-effectiveness means. It does not mean a strategy is necessarily cheap, affordable, money-saving, or likely to fit into the health-care economics of a given country. Cost-effective means only that a strategy is "a good value" relative to other accepted strategies or the strategy it may replace, according to the American College of Physicians (ACP).³⁴ Results of cost-effectiveness analyses depend on the quality of the input data, the strength of assumptions the analysts make, and the validity of their formulas. Also, the ACP notes, "the very notion of cost-effective requires a value judgment—what you think is a good price for an additional outcome, someone else may not."³⁴

But even if everyone agrees that universal adult HIV screening is "a good value," a critical question remains: Where will we get the money to pay for it? An impressive set of US HIV modelers tackled that question in 2010, asking how more frequent HIV testing will affect government discretionary programs (like the Ryan White CARE Act and its AIDS Drug Assistance Program, ADAP) and entitlement programs (like Medicaid and Medicare).³⁵

This analysis relied on data from multiple sources and made sundry assumptions to project the

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impact of shifting from current adult US testing rates (set at once every 10 years) to expanded testing (set at once every 5 years). The investigators did not consider people with private insurance or those eligible for Veterans Affairs care. They distinguished between entitlement and discretionary programs because entitlement program budgets expand in response to ballooning case loads, while discretionary programs have set annual allocations, which make them “more vulnerable to unexpected increases in the number eligible for care.”³⁵ Indeed, anyone familiar with recent ADAP outlays knows that program’s beneficiaries are already squeezed by budgetary belt tightening.

These researchers calculated that 50.1 million HIV-negative adults without private insurance or VA benefits were eligible for discretionary or entitlement programs in 2009, along with 711,000 HIV-positive adults aware of their infection, 189,000 people with undiagnosed HIV infection, and 46,000 with incident (newly diagnosed) HIV infection.³⁵ If HIV screening continues at the current average of once every 10 years, testing would detect an additional 177,000 cases through 5 years, whereas doubling the screening rate to once every 5 years would detect another 46,000 infections on top of that (**Figure 3**). The current testing scheme would cost \$83.7 billion over the next 5 years, and more frequent testing would add another \$2.7 billion.

Impact of current versus expanded HIV screening 2009-2013

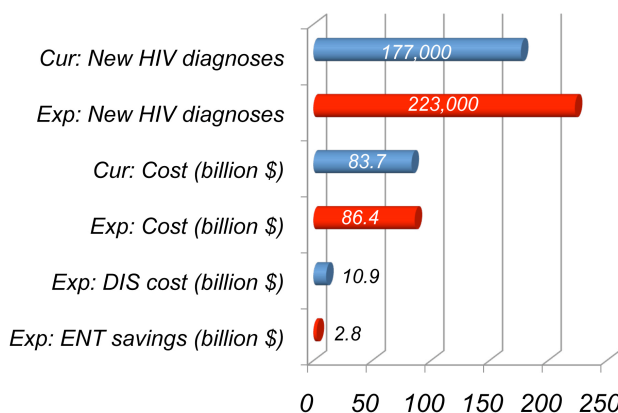


Figure 3. A cost projection by academic researchers determined that expanded (**Exp**) HIV screening (testing every 5 years) would result in 46,000 new HIV diagnoses compared with current (**Cur**) screening (testing every 10 years) from 2009 through 2013. Expanded screening would cost an extra \$2.7 billion over those 5 years, adding \$10.9 billion to spending by discretionary (**DIS**) programs (like ADAP) while saving \$2.8 billion in spending by entitlement (**ENT**) programs (like Medicaid and Medicare).³⁵

Compared with testing for HIV every 10 years, according to this model, testing every 5 years would add \$10.9 billion to the cost of discretionary programs through 2013 while saving entitlement programs \$2.8 billion. Thus entitlement program savings would not offset the higher discretionary program tally. Most of the increased cost would come in spending on drugs, as thousands more people become eligible for antiretroviral therapy. The investigators calculated that the drug price tag would quadruple from \$0.2 billion under current screening practice to \$0.8 billion with expanded screening.

Entitlement programs like Medicaid and Medicare would save money with expanded screening, the researchers explained, because diagnosing HIV earlier in the disease course would shave costs for hospital care and treating opportunistic diseases. Most people diagnosed with expanded screening would be younger and have less advanced disease, so they would more likely get covered through discretionary programs.

These researchers reckoned that expanded HIV screening would cost government-financed testing programs an additional \$503 million over 5 years, almost 10 times more than the \$53 million budget boost proposed for all CDC HIV prevention and surveillance work in the current fiscal year. "If expanded screenings were implemented consistent with the CDC guidelines," the authors concluded, "the policy may not be feasible without additional funds from state and local governments."³⁵ Expanded HIV screening will not have the intended beneficial impact, they argued, "unless government programs have sufficient budgets to expand testing and provide care for newly identified cases."³⁵

A research review by Kaiser Family Foundation investigators bolsters the contention that people diagnosed in a wider US HIV screening program will probably have to lean heavily on discretionary programs.³⁶ "They are likely to have a disproportionately lower income, to be uninsured and/or reliant on public-sector health care coverage, and to be people of color, particularly black individuals," the Kaiser researchers wrote. And because of these demographics, their care costs will probably be compounded by comorbidities like hepatitis, mental illness, and drug dependence.

Clinical consequences of late HIV diagnosis

The clinical impact of delayed diagnosis is easier to calculate than cost because the numbers are there for the parsing in well-designed cohort studies. For example, analysis of 16,375 heterosexuals diagnosed with HIV in England and Wales from 2000 through 2004 had CD4 data on 10,503 people, 4425 (42%) of whom did not get diagnosed until their CD4 count sagged below 200 cells/mm³.³⁷ In this late-diagnosis group, 6.1% died within a year of their positive HIV test, compared with 0.7% of people diagnosed with more than 200 cells/mm³ ($P < 0.01$). These investigators calculated that earlier diagnosis would have cut 1-year mortality by 56% and overall mortality by 32% between 2000 and 2004. The 2564-person Spanish study discussed earlier determined that delayed HIV diagnosis multiplied the death risk by 5.2 (95% CI 1.9 to 14.5).²⁶

A 5494-person analysis of the Netherlands ATHE-NA cohort linked more frequent HIV testing to lower mortality and to higher pretreatment CD4 count.³⁸ Focusing on people infected during sex,

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ATHENA investigators divided cohort members into three groups: **group 1:** no negative test before a first positive test; **group 2:** 1 to 2 years between last negative and first positive test; **group 3:** less than 1 year between last negative and first positive test. Mortality in the 4067 people in group 1 was 1.33 per 100 person-years. Compared with them, the 1561 people in group 2 had a 50% lower risk of death (relative risk 0.50, $P = 0.04$), while the 866 people in group 3 had a 51% lower risk (relative risk 0.49, $P = 0.04$). Almost half of group 1 (48%) had a CD4 count below 200 cells/mm³ when starting antiretroviral therapy. Risk of a sub-200 CD4 count was 57% lower in group 2 and 63% lower in group 3 ($P < 0.0001$ for both comparisons).

UK Collaborative HIV Cohort (CHIC) Study investigators published a novel analysis comparing 2741 “late presenters” (CD4 count below 200 cells/mm³ at diagnosis and when starting therapy), 947 “late starters” (CD4 count above 350 cells/mm³ at diagnosis and below 200 cells/mm³ when starting therapy), and 1290 “ideal starters” (CD4 count above 350 cells/mm³ at diagnosis and between 200 and 350 cells/mm³ when starting therapy).³⁹ Median CD4 gains after 48 and 96 weeks of treatment were significantly lower in late presenters than in late starters, and late presenters had a doubled risk of clinical progression in the first year of therapy compared with late starters (OR 2.04, 95% CI 1.19 to 3.51, $P = 0.01$).

In 2006 the CDC estimated a 3.5 times higher HIV transmission rate from US residents unaware of their infection than from people who knew that had HIV.⁴⁰ Many studies show a higher

risk of HIV transmission from people with higher viral loads. Thus, reason suggests, diagnosing and treating HIV during acute infection (when viral loads are highest) or earlier in the course of chronic infection (when viral loads are lower than in late infection) should slice the risk of HIV transmission. The recently ended HPTN 052 trial offered hard evidence supporting that hypothesis.⁴¹ This international randomized trial calculated a 96% lower risk of HIV transmission when the infected partner in an HIV-discordant couple began antiretrovirals immediately rather than waiting until the CD4 count dropped below 250 cells/mm³.

A province-wide study in British Columbia yielded data showing more HIV testing, more people taking antiretrovirals, more people with undetectable viral loads, and fewer new HIV infections from 1996 through 2009.⁴² Over the study period the number and rate of HIV tests rose from 137,585 per year in 1996-1999 (3.5% of the population), to 139,464 per year in 2000-2003 (3.4% of the population), and to 168,924 in 2004-2008 (4.0% of the population). From 1996 through 2009, the number of people taking combination antiretrovirals soared from 837 to 5413 per year ($P = 0.002$) while the number of new HIV diagnoses waned from 702 to 338 per year ($P = 0.001$). The investigators calculated a strong negative correlation between number of treated people and number of new HIV diagnoses (-0.89 , $P < 0.0001$). Among people who ever had a viral load test, the proportion with a load below 500 copies/mL jumped from under 10% in 1996 to over 50% in 2009 ($P < 0.0001$). A drop in unprotected sex did not explain the falling HIV diagnosis rate since newly reported cases of syphilis, gonorrhea, and chlamydia rose.

A study in San Francisco also saw a link between falling “community viral load” and fewer new

HIV diagnoses.⁴³ San Francisco Department of Public Health investigators calculated mean community viral load (average of most recent viral loads for all HIV-positive people) and total community viral load (sum of most recent viral loads in all HIV-positive people). Both sank significantly from 2004 through 2008 ($P = 0.037$ and $P = 0.021$). In tandem, new HIV diagnoses fell from 798 in 2004 to 434 in 2008. Both mean and total community viral load were significantly associated with new HIV diagnoses over the study period ($P = 0.003$ and $P = 0.002$).

Other studies have yielded similar results. Lower community viral load among Vancouver injection drug users predicted HIV incidence independently of unsafe sex and needle sharing.⁴⁴ Researchers in Taiwan charted a 53% drop in HIV transmission after the country started providing free antiretrovirals.⁴⁵ Because syphilis incidence did not change in the same period, a dip in unsafe sex did not appear to explain the dwindling HIV transmission rate.

Of course the associations documented in these studies do not mean that more frequent testing or lower group viral loads are the only reasons, or even the major reasons, for drops in new HIV diagnoses. These studies offered some evidence that safer sex during the study period did not account for lower HIV incidence. But a list of confounding variables is not hard to imagine: Stronger antiretroviral regimens with a higher barrier to resistance, more serosorting, better needle exchange programs, better care for marginalized groups, and other factors could also contribute to falling rates of new HIV infection. Still, results like these buttress the rationale for more frequent HIV testing, followed by prompt treatment. And conclusive early results of the randomized HPTN 052 trial (described above), although largely de-

pendent on data from Africa, Brazil, India, and Thailand, argue strongly for the impact of earlier treatment on preventing transmission.⁴¹

Proponents of more frequent HIV testing argue that people who know they carry the retrovirus are less likely to have risky sex, at least with partners they believe to be HIV-negative. But some peer-reviewed evidence indicates that HIV-positive people taking antiretrovirals may forsake condoms since they assume they will not pass the virus to sex partners because they have a low or undetectable viral load.⁴⁶⁻⁴⁹ French researchers documented a doubling of HIV risk behaviors among HIV-positive heterosexual men since 2006.⁴⁹ Because antiretroviral treatment for at least 6 months or a viral load below 400 copies/mL also predicted risky sex in this group, the investigators speculated that the doubled rate of unsafe sex “may be related to increasing awareness of the ‘treatment-as-prevention’ concept.”

A CDC meta-analysis tried to gauge how knowing one’s HIV status affects chances of unprotected anal or vaginal intercourse.⁵⁰ This study is now 6 years old, but it did yield data showing that people who knew they carried HIV had unprotected sex less often than people who did not know their HIV status. The CDC team weighed data from eight studies presented from January 1987 through January 2004. In an analysis considering unprotected intercourse with HIV-negative partners, knowing one’s HIV status lowered the chance of risky sex 68%.

Reconciling differences in these types of studies is impossible because of the differing populations analyzed and methods used. Few would disagree that sexual behavior by people who know their HIV status varies from person to

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person and from one sexual foray to the next. Chance and vicissitude may have more to do with donning a condom than moral precepts about transmission risk.

Why physicians don't test for HIV infection

The HIV literature is rife with studies examining why US physicians don't test people for the retrovirus. Most reasons fall into three broad groups:

physicians don't have the time,⁵¹ they won't get paid,⁵¹ or they don't perceive a risk.⁵²⁻⁵⁵

Lack of perceived risk is the stumbling block the CDC hopes to remove with its advice to screen all teens through 64-year-olds who cross paths with a healthcare professional. Yet a 10-year retrospective study at a Boston center figured that all of 221 people who eventually tested positive had one or more "triggers" (such as patient traits,

Table 3. Physician barriers to HIV testing in three clinical settings⁵¹

<i>Shared by prenatal clinics, emergency departments, and other settings</i>	<i>Shared only by prenatal clinics and emergency departments</i>	<i>Shared only by prenatal clinics and other settings</i>	<i>Shared only by emergency departments and other settings</i>
<ol style="list-style-type: none"> 1. Insufficient time 2. Consent process 3. Lack of knowledge or training 4. Language 5. Lack of patient acceptance 6. Pre-test counseling requirements 7. Competing priorities 8. Inadequate reimbursement 	<ol style="list-style-type: none"> 1. Informing an HIV-positive patient 2. Institutional costs 	<ol style="list-style-type: none"> 1. Low-risk patient population 2. Fear/concern of offending patient 	<ol style="list-style-type: none"> 1. Patient confidentiality concerns 2. Post-test counseling requirements 3. Cultural barriers 4. Concern about patient follow-up 5. Lack of HIV-related referral networks 6. Not appropriate for provider to test
<p><i>Barriers in "other settings" not shared by prenatal clinics or emergency departments</i></p>			
<ol style="list-style-type: none"> 1. Lack of trust/relationship with patient 2. Gender difference between provider and patient 3. Difference in sexual orientation/lack of knowledge regarding sexual orientation 4. HIV/STDs not an issue in my patients/community 5. HIV risk factors don't relate to the care I provide 6. Lack of institutional policies that encourage testing 7. Lack of outreach to adolescents 			

symptoms, and physical findings) that should have prompted physicians to recommend HIV testing earlier.⁵⁵ But these people made a median of five medical visits before their first positive HIV test. These findings suggest that if health-care professionals aren't going to follow CDC screening guidelines, they should print out this trigger list (**see link at reference 55**) and pin it someplace prominent.

A 2007 study of physicians' excuses for not testing relied on a review of recent literature, meeting abstracts, and other sources.⁵¹ The investigators excluded non-US studies and those that sized up only patients' reasons for eschewing HIV tests. They grouped physician-related barriers to care into three settings: prenatal clinics, emergency departments, and all other medical settings, including internal medicine, sexually transmitted infection (STI) clinics, and adolescent clinics. This survey disclosed 41 reasons for not testing: 24 in prenatal clinics, 20 in the emergency department, and 23 in other settings. Feeble imagination seems to be the only factor limiting perceived or fancied reasons for not testing. All three settings shared eight barriers (**Table 3**). The authors proposed that "some or all of these barriers must be addressed before the CDC recommendation for routine HIV testing can be realized in all US medical settings."

Strategies for earlier HIV testing

A half-decade ago, opt-out HIV testing for all adults and adolescents regardless of perceived risk became the CDC-sanctioned strategy to diagnose positive people earlier.⁵ But even if physicians and other potential testers adopt this approach, they should take other steps to make sure it works. Reviewing tactics to promote earlier diagnosis of HIV, David Hardy, a seasoned HIV clinician in Los Angeles, advised colleagues

to do two things before taking a more aggressive testing stance.⁵⁶ First, they must understand regional and state HIV testing laws. Second, they must develop a testing strategy that relies on a particular HIV test with a set policy for confirmatory testing. When telling patients they will be tested for HIV as part of routine care, healthcare professionals should explain that any sexually active person may be at risk for HIV and assure patients that results will remain confidential. In the interview in this issue, the CDC's Bernard Branson outlines steps institutions should take when implementing opt-out HIV testing.

Other experts and investigators have offered suggestions on early testing strategies that do not specifically involve universal opt-out testing:

- Take advantage of rapid testing technologies to provide results during the testing visit.⁵⁷
- Consider nurse-initiated streamlined counseling and rapid testing.⁵⁸
- Be aware of barriers to HIV testing in specific groups to provide testing opportunities suitable for specific communities.⁵⁷
- Ensure that HIV testing is offered routinely in settings that routinely care for high-risk individuals, including STI clinics, clinics that care for people with viral hepatitis, and drug addiction services.⁵⁹
- Test partners of people diagnosed with HIV.⁵⁹
- Devise social network strategies to identify people at high risk of HIV infection and encourage them to get tested for HIV.⁵⁹
- Take steps to reduce stigma associated with HIV testing.⁵⁹

In 2010 the Obama administration announced a National HIV/AIDS strategy for the United

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States that sets out three steps to lower the new infection rate, along with three targets to hit by 2015 (**Table 4**).⁶⁰

Universal opt-out testing: pros and cons

The CDC laid out an exhaustive rationale for universal opt-out HIV screening in the original recommendations⁵ and in later comments:⁷ (1) Health professionals may perceive risk assessment and counseling, which are not part of the new guidelines, as too time consuming. (2) Routine screening helps remove the stigma of HIV testing. (3) The demographics of HIV infection have changed, and many groups now at risk

(women, heterosexuals, rural residents) may not perceive this risk. (4) Many HIV-positive people access health care but remain untested until they have symptoms. (5) Routine HIV testing is an effective prevention intervention. (6) The 20% to 25% of people unaware of their HIV infection account for about half of new infection transmissions. (7) CDC data from 2002-2003, before the new guidelines, showed that the largest proportion of HIV tests were done in doctors' offices (44%), but testing in doctors' offices yielded only 17% of all positive tests. In contrast, tests in hospitals (including emergency departments) accounted for 22% of all tests and 27% of positive tests, tests in public community clinics accounted for 9% of all tests and 21% of positive tests, and tests in HIV counseling and testing facilities accounted for 5% of all tests and 9% of positive tests.

Table 4. US National HIV/AIDS strategy to reduce HIV incidence⁶⁰

Recommended action steps	Targets by 2015
1. Intensify HIV prevention efforts in communities where HIV is most heavily concentrated.	1. Lower the annual number of new infections by 25% (from 56,300 to 42,225).
2. Expand targeted efforts to prevent HIV infection using a combination of effective, evidence-based approaches.	2. Reduce the HIV transmission rate (a measure of annual transmissions in relation to the number of people living with HIV) by 30%, from 5 persons infected each year per 100 people with HIV to 3.5 persons infected each year per 100 people with HIV.
3. Educate all Americans about the threat of HIV and how to prevent it.	3. Increase from 79% to 90% the percentage of people living with HIV who know their HIV status (from 948,000 to 1,080,000 people).

But not everyone agrees that universal opt-out screening makes sense for the United States or countries with similar epidemics. Although some studies figure opt-out testing would be cost-effective,³⁰⁻³² at least one cost-benefit analysis reckoned that targeted HIV counseling and testing would cost less, diagnose more new HIV infections, and prevent more infections than untargeted opt-out testing³³ (see “How much does late diagnosis cost” above). Another study found that doubling the HIV testing rate in the United States would stick discretionary programs (like Ryan White) with an added \$10.9 billion in costs over the next 5 years, without saving entitlement programs (like Medicaid and Medicare) nearly as much.³⁵

Beyond questions of cost and effectiveness lies the boggy terrain of legality. A 2011 review of state HIV screening laws found that 46 jurisdictions, including Washington, DC, were compatible with the 2006 CDC recommendations, while 5 states were incompatible on at least one measure.⁶¹ For some states, compatibility varied by health care provider, setting, scenario, or type of law. This review did not include case laws or policies issued by other regulatory agencies, such as health departments.

An expert from the Center for HIV Law and Policy warned in 2007 that “rigid application of the new [CDC] guidelines may trigger legal claims, especially if there is no link to care for persons with a positive test result, no proof of informed consent, or inadequate counseling.”⁶² In an interview in this issue of *RITA!*, the CDC’s Bernard Branson says the agency has had no reports of “people suffering adverse consequences or being tested without their permission” in the 5 years the revised guidelines have been in place.

Are US patients opting out or staying in?

The ultimate question about the CDC’s opt-out screening plan is whether people are opting in or out. Twenty recent surveys reported from diverse clinical venues suggest acceptance rates often lie above 50%—sometimes *well* above 50%—in community health centers, hospital emergency departments, and jails.

Three studies from **community health centers** found widely different acceptance rates—67% in a six-clinic study in North Carolina, South Carolina, and Mississippi,⁶³ 58% in a South Carolina clinic serving both urban and rural residents,⁶⁴ and 35% in a Bronx, New York clinic.⁶⁵ A key difference in the three studies is that the first two offered a rapid HIV test^{63,64} while the Bronx study used a standard assay requiring venipuncture. The CDC guidelines do not specifically call for rapid testing, but these studies suggest offering on-the-spot results has a clear advantage. In the Bronx, younger age, Hispanic ethnicity, and having another blood test at the same visit independently raised chances that people would say yes to opt-out testing.⁶⁵ In the six-center study, the number of people offered testing jumped from 3000 in the year before the clinics adopted the CDC strategy to about 16,000 in the year afterwards.⁶³ But the 16,000 people offered testing still represented only 28% of patients between 13 and 64 years old.

A 60-person randomized trial involving **STI clinic** patients who had declined HIV testing in Syracuse, New York found that brief behavioral counseling yielded a higher rapid testing rate than an educational video, but acceptance rates were low with both interventions (45% versus 19%).⁶⁶ Over-

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all uptake of opt-out HIV screening at a London STI clinic stood at 53% ($n = 573$).⁶⁷ This acceptance rate marked a hefty improvement from the 18% rate recorded before introduction of opt-out testing, nurse-performed asymptomatic genitourinary screening, mail delivery of HIV results, and the end of routine pre-HIV test counseling.

Among 3467 **hospital inpatients** offered opt-out rapid HIV testing at a Veterans Affairs hospital in Washington, DC during a 17-month period, only 824 (24%) agreed to testing.⁶⁸ At a Boston teaching hospital, the debut of routine voluntary HIV testing more than tripled the chance that inpatients would get tested when compared with earlier risk-based testing.⁶⁹ Routine testing yielded approximately 2 new HIV diagnoses per month, compared with 1 per month during the control period.

A May-June 2004 study at 14 geographically diverse **antenatal clinics** funded by the Ryan White CARE Act found that 90% of 853 women offered opt-out HIV testing accepted, and 91% reported feeling comfortable with testing.⁷⁰ Feeling comfortable was linked to greater knowledge about HIV. Antenatal opt-out screening proved even more successful at a public hospital in Denver, where 12,000 of 12,221 women (98.2%) agreed to get tested.⁷¹ Median time to delivery was 1 day among women who opted out compared with 176 days among women who agreed to testing ($P < 0.001$).

A study of people entering New York City **jails** in 2006 found that 6411 of 9305 (69%) agreed to rapid HIV testing.⁷² Among 33,162 people entering jail in Washington, DC from June 2006 through May 2008, 22,515 (68%) agreed to opt-

out HIV testing.⁷³ A randomized study of 323 women sequentially admitted to a Connecticut jail recorded a significantly higher opt-out testing acceptance rate in women offered testing the day after admission (73%) than in women offered testing on the day of admission (55%) or 7 days after admission (50%).⁷⁴ Younger age and a lower likelihood of early release favored agreeing to HIV testing. Despite these high acceptance rates, researchers say “the vast majority of jails in the United States do not screen routinely for HIV or STIs.”⁷⁵

Hospital-based dental clinics may be an overlooked HIV testing venue. Using a counselor-based (not opt-out) approach to offer rapid HIV testing at New York City’s Harlem Hospital Center dental clinic in March 2008, researchers registered an acceptance rate of 97.6% in more than 3500 dental patients approached.⁷⁶ Self-reported HIV risk behaviors included recent unprotected heterosexual intercourse in 73.5%, recent or past injection drug use in 4.6%, and gay sexual orientation in 2.6%.

Much interest has focused on rapid opt-out testing in **hospital emergency departments**, partly because poor people with a high HIV risk often use emergency rooms for primary care. At a public safety-net hospital in Denver, researchers compared HIV testing and prevalence rates with opt-out testing versus physician-directed testing during sequential 4-month intervals between April 2007 and April 2009.⁷⁷ During the opt-out phase, 6933 of 28,043 people (24.7%) completed testing and 0.5% had HIV infection. During the physician-directed phase, 243 of 29,925 people (0.8%) completed testing and 0.01% had HIV infection. Nontargeted opt-out screening more than tripled the chance of a new HIV diagnosis (risk ratio 3.6, 95% CI 1.2 to 10.8).

A study of 1959 people offered routine HIV testing at a Boston hospital emergency department recorded an acceptance rate of 71%.⁷⁸ Independent correlates of refusing HIV testing included female gender, household income above \$50,000, lack of self-perceived HIV risk behavior, having a previous HIV test, and enrollment during morning hours. In the emergency department at the Medical College of Georgia, 5080 of 5585 people from 13 to 64 years old (91%) offered opt-out testing agreed to a rapid test from March 2008 to January 2009.⁷⁹ White and married people were significantly less likely to accept testing than black or single people, and adults were twice as likely to accept as adolescents. The acceptance rate rose as age increased among adolescents, whereas the rate fell as age increased among adults.

At a university hospital emergency department in Washington, DC, 2476 of 4151 people (60%) offered rapid opt-out screening over 3 months in 2006 agreed.⁸⁰ Older people, Asians, and nonlocal people were more likely to decline testing, while African Americans were marginally more likely to accept testing. In a later report from this same emergency department, 5232 of 9826 people (53%) accepted rapid opt-out screening.⁸¹ Acceptance rates were similar among blacks (55%), whites (52%), and Hispanics (50%), but lower for Asians (42%). The most frequent reasons for declining testing were lack of perceived risk (in 49%) and a recent HIV test (in 18%).

In a Chicago hospital emergency department, 2824 of 4849 people (58%) offered a rapid whole-blood HIV test regardless of risk in 2003-2004 accepted testing.⁸² Among 35 screened people who had a positive test (1.2%), 18 (51%) reported no traditional HIV risk factors. Fourteen of 31 people (45%) with CD4 counts available had fewer than 200 cells/mm³.

Researchers working with a large pediatric emergency department in Memphis, Tennessee developed an opt-out screening procedure through surveys of 118 health care providers, most of whom (78%) did not know about the CDC's opt-out guidelines (in 2008), and most of whom (58%) predicted that routine screening would fail in adolescents because of parent or guardian refusal.⁸³ However, only 13% of 2002 adolescents from 13 to 18 years old opted out. Adolescents 15 or older were less likely to opt out.

Across the United States, the CDC reports, the proportion of people getting tested for HIV began to climb around 2006, the year the Centers called for opt-out screening.¹⁰ The CDC estimated that the percentage of 18- to 64-year-olds ever tested for HIV stayed flat at about 40% from 2001 to 2006, then climbed to 45% through June 2009. That uptick may be the best indicator that health professionals have begun to heed the CDC's call for wider HIV screening—and that people are not opting out.



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Summary points on late HIV diagnosis

1. Of an estimated 1.1 million HIV-positive people in the United States, 1 in 5 remains undiagnosed.¹
2. In 2006 the CDC revised its HIV testing advice to recommend that everyone between 13 and 64 be offered opt-out testing at any medical encounter, unless prevalence of undiagnosed HIV in the area lies below 0.1%.⁵
3. An estimated 32% of Americans diagnosed with HIV in 2008 had AIDS within 12 months.⁸
4. In a 2007 US-Canadian cohort study, median CD4 count at HIV diagnosis stood 33 cells/mm³ below the 350-cell antiretroviral-start threshold of that time.¹¹
5. Factors that predict delayed diagnosis in several studies include older age, nonnative birth, and HIV acquisition during heterosexual sex or by injecting drugs rather than during sex between men.
6. Several studies found that universal opt-out HIV testing is cost-effective,³⁰⁻³² but not all studies reached that conclusion,³³ and some research indicates that wider HIV testing in the United States would put a much heavier burden on discretionary programs like Ryan White and “may not be feasible without additional funds from state and local governments.”³⁵
7. Studies have linked late HIV diagnosis to slower CD4 gains, more new AIDS diagnoses, or higher mortality.³⁷⁻³⁹
8. Lower “community viral load” attributed to wider HIV testing and antiretroviral use has been tied to lower HIV incidence or transmission.⁴²⁻⁴⁴
9. Strategies to promote earlier HIV testing include universal opt-out HIV screening, use of rapid HIV tests, understanding and overcoming patient barriers to HIV testing, partner notification and testing, and reducing test-related stigma.
10. Patient acceptance of opt-out HIV testing varies from study to study, ranging from 35% to 67% in community health centers.⁶³⁻⁶⁵ Studies in hospital emergency departments and jails often report acceptance rates well above 50%.

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Opt-out HIV testing: key questions on cost and implementation

An interview with **Bernard M. Branson, MD**

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Dr. Branson is the lead author of the CDC's recommendations for opt-out HIV screening for adults, adolescents, and pregnant women. He heads CDC activities on new technologies for HIV testing, including rapid HIV tests.



Rationale for opt-out HIV screening and health system impact

Mascolini: What is the CDC's primary rationale for recommending opt-out HIV testing (**Table 1**) for all adults and adolescents seeking medical care?

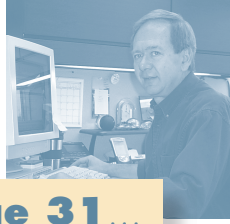
Branson: There are several key reasons for recommending opt-out testing.¹ One is to make testing more routine, because consent for most laboratory tests is based on an opt-out approach. The second reason is to remove potential barriers to testing that might be created by more elaborate requirements for HIV testing. And the third is to

Table 1. Key CDC HIV screening recommendations for patients in all health-care settings¹

- HIV screening is recommended for patients aged 13 to 64 in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.

For more details on the CDC recommendations, see the introduction to the article starting on page 5 of this issue of *RITA*!

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reduce stigma for patients who are undergoing HIV testing. It has been shown that when people perceive that something is offered to everyone as opposed to having some individuals singled out for targeted testing, they feel there's less stigma associated with the testing.

Mascolini: Can the US healthcare system absorb the direct cost of universal opt-out testing, as well as the cost of treating the many additional people who will presumably test positive?

Branson: I can't comment directly on all the costs, but I think it's important to point out that identifying HIV-positive people through testing does not create the expense. In other words, regardless of whether an infected person is tested, their need for treatment already exists, and they will still receive treatment when they are eventually diagnosed.

Usually, if a person presents later in the course of the disease, they're sicker and it's more expensive to take care of them than if they had been tested and diagnosed earlier, when they could have received optimal benefit from treatment. Some studies have shown that overall costs are lower when people are diagnosed earlier because they avoid hospitalizations and costs for more serious clinical events.²⁻⁴

Mascolini: AIDS Drug Assistance Programs (ADAPs) that help poor people pay for antiretrovirals are cutting back in several states. What will happen when more young, poor people who will need ADAP get diagnosed with HIV?

Branson: Again, I can't comment specifically on how wider HIV testing might influence ADAP support. We're in a state of change right now with healthcare reorganization in this country, and potential changes could affect eligibility for other programs like Medicaid. So I think it's difficult to predict exactly how care will be paid for if more people are diagnosed with HIV.

We do anticipate that identifying HIV-positive people earlier and giving them effective treatment that is likely to make them less infectious will in the long run decrease the number of people who will need treatment. That is the philosophy of the test-and-treat strategy that has been getting so much attention.^{5,6}

One of the goals of the National AIDS Strategy⁷ is to increase the number of people who are diagnosed and to increase the number of people who are in treatment. I think opt-out testing recommendations are designed to address both of those goals.

Cost-benefit and legal questions with opt-out HIV testing

Mascolini: Some cost-benefit analyses figure that universal opt-out testing is a good value in various scenarios.⁸⁻¹⁰ But one cost-benefit study determined that risk-based testing would diagnose more HIV cases than opt-out testing and prevent more HIV infections at a lower gross cost per infection averted.¹¹ Can you summarize the arguments you made against this analysis in *PLoS Medicine*?¹²

Branson: First of all, I don't think HIV testing is an either/or question. In other words, there's not just one approach that should be applied.

Nor is that the CDC's position. We believe expanded opt-out screening in healthcare settings will help detect HIV in people who would otherwise go undiagnosed. We're not proposing abandoning targeted testing for people at high risk and in particular for some people at very high risk who need to be retested periodically. Both strategies are necessary.

The model David Holtgrave developed¹¹ incorporates some assumptions that can be questioned—for example, that you can identify for testing, at no additional cost, a high-risk population with an HIV prevalence of 10%. Our studies show that seeking out a high-prevalence population for targeted testing is costly in terms of cost per test: You have to spend money to find those people, whereas there is a much smaller incremental cost for general HIV screening in healthcare settings because people are already coming in and seeking care in those settings.

Another important question involved in Holtgrave's analysis is the assumed prevention benefit of the counseling associated with HIV testing. The US Preventive Services Task Force reviewed behavioral interventions for sexually transmitted diseases including HIV and found no evidence that brief interventions similar to the kind that would be offered with an HIV rapid test have long-term benefits in changing behavior of people who test negative. More intensive interventions are necessary to have that kind of behavioral benefit.

I think those two factors—the cost associated with targeted HIV testing and the question of exactly how much benefit there is from the brief counseling offered with an HIV test—can explain the differences between Holtgrave's conclusions and the conclusions of several other

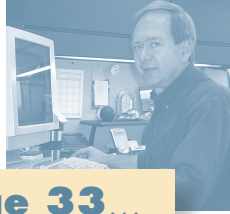
models that focused more on detecting people with HIV infection and the benefits of getting them into treatment.

Mascolini: Are there legal risks in making opt-out testing standard of care in a medical practice or hospital—especially in regard to informed consent, counseling, and linkage to care?

Branson: I think the legal risks go in two directions. Certainly there could be legal risks when a person is infected with HIV but the infection goes undetected because that person was not offered testing.

When you consider issues related to informed consent, one reason opt-out testing is recommended for healthcare settings and not for nonclinical settings is that healthcare settings already operate under a doctrine of informed consent. You can't do any procedure for a person in a healthcare setting without their consent. So the question with opt-out HIV testing is whether you need a separate, more elaborate written consent documenting that a person consents to HIV testing. Evidence from many places shows that separate written consent does not confer additional legal protection.

The opt-out recommendations have now been in place for 5 years, and we do not have evidence or reports of people suffering adverse consequences or being tested without their permission. We are confident that opt-out screening has not resulted in that kind of problem. In areas or institutions that have a long history of a separate process for HIV testing, the attorneys involved may wish to perpetuate that separate process, but we are not seeing that this provides a legal benefit to the institution.



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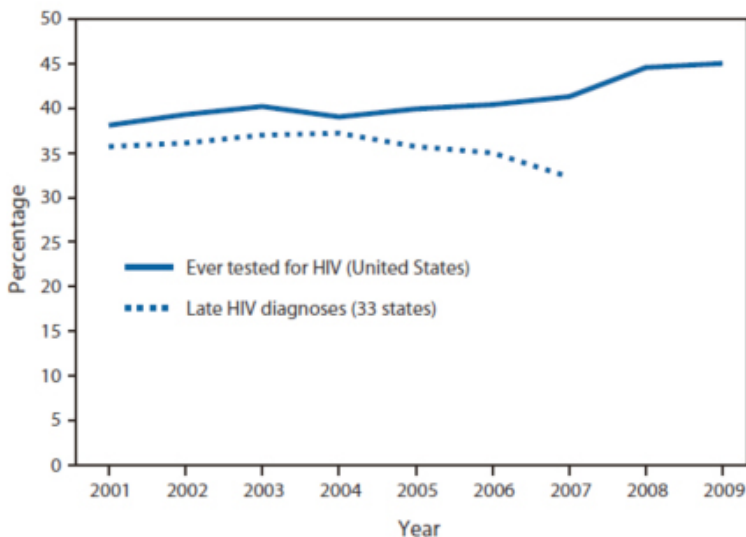
Advice on adopting opt-out HIV screening

Mascolini: Are US healthcare professionals adopting this strategy?

Branson: What I can say certainly is that professional organizations like the American College of Physicians and the American College of Obstetricians and Gynecologists have issued very similar recommendations to their members for HIV screening.

“In 2009 a record 82.9 million adults in the US reported having ever been tested for HIV infection—an increase of 11.4 million people since the CDC recommendations were issued in 2006.”

A CDC analysis showed that the proportion of Americans who said they’d been tested for HIV remained stable at 40% from 2001 to 2006, but then rose to 45% in the 3-year period from 2006 to 2009 (**Figure**).¹³ In 2009 a record 82.9 million adults in the United States reported having ever been tested for HIV infection. That represents an increase of 11.4 million people since the recommendations were issued in 2006. And we have numerous reports from groups that have initiated opt-out HIV screening programs.



Percentage of persons aged 18-64 years who reported ever being tested for HIV (United States, 2001-2009), and percentage of late HIV diagnoses (AIDS diagnosis within 12 months of initial HIV diagnosis) (33 states, 2001-2007). (Reproduced from: Centers for Disease Control and Prevention. Vital signs: HIV testing and diagnosis among adults--United States, 2001-2009. *MMWR Morb Mortal Wkly Rep.* 2010;59(47):1550-1555.¹³)

All of this suggests that at least some healthcare professionals are adopting these recommendations. We always expected adoption and implementation to be incremental. We didn't think that everyone would just begin screening universally the year after the recommendations came out. But I do think we have evidence that they are being adopted.

Mascolini: If an institution decides to implement opt-out testing, what steps should it take to put this policy in place?

Branson: The most important first step is to get buy-in from all the stakeholders involved, both people in the institution and in the community. Also, for each institution, questions related to nursing, standing orders, and the laboratory, for example, must be addressed and solutions designed that are specific to the needs of that institution.

The CDC recommends that people receive information about HIV at the time they are tested, so there has to be a mechanism to deliver that information, whether with a pamphlet, a handout, or a video (**Table 2**). Similarly, people need to be advised that they have an opportunity to decline testing. Many institutions have done this with a separate information sheet that might say an HIV test is recommended as part of your care, here are the reasons for it, and if you don't want this test you should sign this and give it to one of the health care providers. I think those are necessary steps in the process of implementing opt-out testing.

When CDC's recommendations came out, there was some confusion about whether CDC was recommending opt-out HIV testing or recommending rapid testing. Many places assumed that they have to do rapid point-of-care testing to implement these recommendations. Rapid

Table 2. CDC advice on consent and pretest information¹

- Screening should be voluntary and undertaken only with the patient's knowledge and understanding that HIV testing is planned.
- Patients should be informed orally or in writing that HIV testing will be performed unless they decline (opt-out screening). Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions and to decline testing. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as are other screening or diagnostic tests; a separate consent form for HIV testing is not recommended.
- Easily understood informational materials should be made available in the languages of the commonly encountered populations within the service area. The competence of interpreters and bilingual staff to provide language assistance to patients with limited English proficiency must be ensured.
- If a patient declines an HIV test, this decision should be documented in the medical record.

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testing is not part of the recommendation. Rapid testing may be important in settings where patients are unlikely to receive their results otherwise. But with the newer technologies available today, a conventional test can produce results in an hour or less, so it is not always necessary to use a point-of-care rapid test.

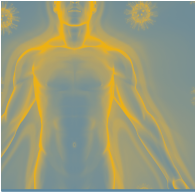
Mascolini: Are there other points you would like to add on any of these issues?

Branson: I think an important point is that programs that are implementing these recommendations are in fact identifying people who

have undiagnosed HIV infection. The recommendations are having the desired outcome—getting more people tested and getting more people linked into services where they can access treatment. And that treatment will have a substantial impact on improving their life expectancy and potentially in decreasing the likelihood that they will transmit HIV to others. I think the bottom line is that evidence accumulating since the recommendations came out indicates that they seem to be working: The number of persons who have been tested is going up, and the number whose HIV is diagnosed late is going down.

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Getting HIV-Positive People Into Care—and Keeping Them There

By Mark Mascolini

If HIV-positive people do get diagnosed, a dismaying fraction gets no care for months or even years. Among 48,413 US residents diagnosed with HIV in 2005 and 2006 in 37 states with name-based reporting, CDC statisticians estimated that only 55% had a CD4 count within 4 to 6 months of diagnosis, and only 64% had their CD4s tallied 19 to 24 months after testing positive (**Figure 1**).¹ Among 38,070 people diagnosed in those states in 2005 and 2006, 31% had neither a CD4 count nor a viral load test within 12 months of diagnosis.

Proportions of people late to care were evenly distributed among people infected during gay sex (30.9%), while injecting drugs (27.7%), either during gay sex or while injecting drugs (28.1%), and during heterosexual sex (32.8%).¹ In the same analysis, a bigger portion of African Americans got to care late (35.0%) than did Hispanics (29.2%) or whites (26.4%).

Linkage estimates both slippery and baleful

Although recent reports offer some data indicating sluggish entry into care after HIV diagnosis, researchers who study this issue say such data are, at best, approximations. Michael Mugavero and colleagues from the University of Alabama at Birmingham point to a simple reason for the sketchy quality of these findings: “the activities of testing and linkage [to care] are often uncoupled.”² That uncoupling also helps explain why linkage remains so poor in the United States and elsewhere.

Research on entry to HIV care suggests the ponderous scope of the problem, while outlining a web of patient- and practice-related factors that contributes to dismal linkage numbers. A study that melded national prescription data with CDC HIV prevalence estimates reckoned that 314,000 of 1,135,000 people diagnosed with HIV in 2008

Time from HIV diagnosis to first CD4 count in US

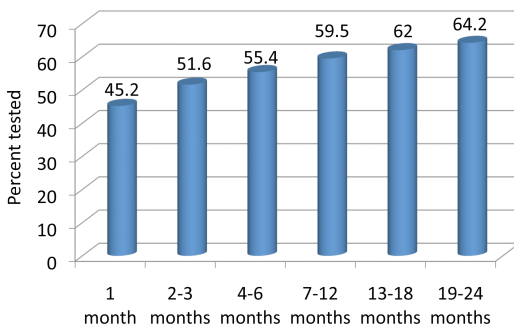


Figure 1. Among 48,413 people in the United States diagnosed with HIV infection in 2005 and 2006, fewer than two thirds had their CD4 count measured 19 to 24 months after diagnosis. This CDC calculation indicates that one third of US residents diagnosed with HIV in those years were getting no care or grossly inadequate care 2 years after testing positive.¹

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(28%) were not getting care for their infection.³ The number of infected people not in care far outstripped the estimated 227,000 US residents with undiagnosed HIV infection.

Massing statistics from 28 entry-to-care studies that collected data from May 2005 through 2009, CDC investigators figured 72% of HIV-diagnosed people in the United States began care within 4 months of diagnosis,⁴ a much higher proportion than the CDC's own calculation of the proportion of people with a CD4 count measured 4 to 6 months after diagnosis—or even 2 years after diagnosis (**Figure 1**).¹ The meta-analysis determined that a higher proportion of people who tested positive in an emergency department than in a community center entered care (76% versus 67%).

Longitudinal study of 1266 people diagnosed with HIV between July 1, 2005 and June 30, 2006 and followed through June 15, 2007 in Philadelphia charted a median 8-month time to entering care, with a range from 1 to 26 months.⁵ Interviews of 1038 HIV-positive people in public hospitals in Miami or Atlanta found that 1 in 5 had not started care for their infection although they knew they had HIV for more than 5 years.⁶ Two in 5 of these people had not seen an HIV clinician for more than 6 months. A study of 1928 people diagnosed with HIV in 2003 in New York City found that 369 (19%) did not have a viral load test or CD4 count within 3 months of diagnosis and 331 (17%) never had a recorded viral load or CD4 count through the end of 2006.⁷

Entry to care is a particular concern for HIV-positive prisoners who may or may not be taking antiretrovirals when released. A retrospec-

tive study of 1750 HIV-positive inmates released from Texas prisons from January 2004 through December 2007 found that only 28% had enrolled in an HIV clinic within 90 days.⁸

Even after HIV-positive people begin care, they report unmet medical and dental needs, according to an analysis of the HIV Cost and Services Utilization Study (HCSUS), the first nationally representative study of people in care for HIV.⁹ Extrapolating from a 2864-person sample of people in care in January 1996, researchers figured that 58,000 of 230,900 HIV-positive people (25%) had unmet medical or dental needs, including 11,600 (5%) who had both unmet medical and dental needs. Low income, lack of insurance, and Medicaid insurance without dental benefits made unmet needs more likely.

Reasons for delayed entry bountiful and linked

Even a cursory review of published studies on starting care for HIV can mine a trove of reasons explaining why diagnosed people don't get to a doctor's office. The literature search for this article readily revealed dozens of predictors, often singled out in multivariate analyses. Three points emerge from this kind of inquest:

- Reasons for delayed entry to care can be divided into two groups—those inherent in a turbid US healthcare system and those reflecting the demographics and behaviors of HIV-diagnosed people.
- Demographic and behavioral reasons are interrelated, ramified, and nearly impossible to tease apart.
- Studies in diverse populations identify race or ethnicity, poverty, lack of insurance, mental illness, and substance abuse as common patient-related reasons for delayed care.

The article that begins this issue of *RITA!* examines one overriding reason HIV-positive people don't start care: they don't know they're infected. But ever-expanding testing will not solve the problem of delayed entry to care. Indeed, some research suggests HIV screening dollars would be better spent making sure people who test positive actually get their results and then making sure they get an HIV clinic appointment and show up for their first exam.¹⁰ This simulation of HIV testing services determined that "interventions that improve the probability of success in later stages in the testing pathway are more cost-effective than investments devoted to earlier stages."¹⁰

Once people get a positive test result, all but the most motivated may quickly run afoul of a healthcare system aptly labeled "fragmented" and "fractured" by physicians who study why people diagnosed with a readily arrested infection do not get themselves quickly to an HIV clinic (**Table 1**).² As Michael Mugavero stresses

in the interview starting on page 64 of this issue, pinpointing and correcting system-wide problems improve care for whole clusters of patients, while pinpointing and correcting individual patient problems help only that individual.

Mugavero and colleagues note that the CDC and local and state health departments run the country's HIV testing and prevention engines.² But treatment and support services rely on the Health Resources and Services Administration, the Center for Medicare and Medicaid Services, and private insurers. "Although varying levels of integration exist within and between service delivery organizations and funding agencies that provide testing and/or prevention and medical and/or supportive services," these experts write, "the vast majority of activities are uncoordinated."²

Even when newly diagnosed people do not suffer from denial or distrust of the whole healthcare system, a range of brass-tack realities may

Table 1. Health system problems that delay entry to care*

- Separate HIV testing and HIV care facilities
- Passive referral to care versus active case management
- Cursory case management after HIV diagnosis
- Lack of readily available support services, such as mental health and substance abuse services
- Longer time between referral and first scheduled visit
- Clinic hours that do not accommodate work schedules and dependant care needs
- Lack of culturally appropriate services in the clinic
- Underfunding of clinics that will see more patients with expanded HIV testing (for example, through the Ryan White CARE Act)
- Health worker shortages and lack of clinicians specializing in HIV care

*Most of these obstacles are reviewed by Mugavero and colleagues.²

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stand between them and a doctor: low income, little or no insurance, lack of transportation, child-care obstacles, depression, drug or alcohol abuse, physical or sexual abuse, getting time off from work, fear of stigma or discrimination, a cascade of competing priorities, and just being too sick. (A CD4 count under 50 cells/mm³ made spotty clinic attendance about 50% more likely in one study of 1286 people with HIV.¹¹) Complicating matters further, barriers to care often differ from one HIV population to another, observes Richard Moore of Johns Hopkins University.¹²

Holes in the health system that delay HIV care

Perhaps the biggest system-related obstacles to smooth entry to care are the walls—literal and figurative—between testing centers and treatment centers. A New York City Department of Health study found that 369 of 1928 people (19%) diagnosed with HIV in 2003 had not started care within 3 months and 331 (17%) never started care during the study.¹³ Compared with people diagnosed at a center that offered both testing and treatment, those diagnosed at stand-alone testing facilities had a 50% to 90% higher risk of delayed care, depending on the type of facility.

At solitary HIV testing units, active case management of people who test positive gets more people into care than passive referral. Analysis of 270 HIV-positive people in the Antiretroviral Treatment Access Study (ARTAS) found that 31% had not seen an HIV clinician within 6 months of their diagnosis.¹⁴ People who received short-term case management were almost 4 times more likely to enter care within 6 months than people merely referred to HIV care.

A 4-city ARTAS analysis randomized 316 people diagnosed from 2001 to 2003 to passive referral or to “intensive, short-term assistance” to help get them into care.¹⁵ Almost two thirds of those receiving short-term help (64%) visited an HIV primary care clinician at least once in two consecutive 6-month periods, compared with 49% of those receiving passive referral (relative risk 1.41, 95% confidence interval [CI] 1.1 to 1.6, $P = 0.006$). The intervention significantly improved linkage to care in 12 of 26 subgroups assessed:

1. Males
2. Hispanics
3. People with less education
4. People within 6 months of their HIV diagnosis
5. Unstably housed people
6. People who reported no usual source of care or who usually used a hospital emergency room
7. People without depressive symptoms
8. People who did not use crack cocaine or inject drugs in the past 30 days
9. People who had not received help from others (such as family or friends) in getting HIV care
10. People in the preparation or action stages of readiness to enter HIV care (versus precontemplation or contemplation stages)
11. People with positive beliefs and attitudes about HIV treatment and care
12. People who did not say feeling well was a reason they did not seek HIV care

The intervention (versus passive referral) appeared to improve linkage (but not significantly) in 10 other groups, while four groups seemed not to benefit at all:

1. People with higher education
2. People with symptoms of depression
3. People who used crack cocaine or injected drugs recently
4. People who had help from others in getting care

A 2006-2009 study of 355 crack users admitted to a hospital in Miami or Atlanta found that not being helped into HIV care at diagnosis almost tripled the risk of never starting HIV care (adjusted odds ratio [AOR] 2.83, 95% CI 1.56 to 5.15).¹⁶ This study also found that lack of treatment for drug abuse quadrupled the risk of failure to start HIV care (AOR 4.13, 95% CI 2.24 to 7.62).

Even when testing centers or clinics have counselors to answer questions and help the newly diagnosed get into care, some people with a new HIV diagnosis say they never met a case manager. An ARTAS study of 316 HIV-positive people not getting medical care found that 55% claimed the counselor did not send them to a case manager, 27% complained that the case manager did not spend enough time with them, and 22% said the case manager did not answer all their questions.¹⁷ Almost one quarter of these people were told—or thought they were told—that they did not need care for their HIV infection.

Longer time between the call to set up an appointment and the appointment itself raises the risk that a new HIV patient won't show up. Focusing on 522 people with a first HIV primary care appointment scheduled between August 2004 and August 2006, the University of Alabama team counted 162 potential patients (31%) who did not come to the clinic within 180 days

of their clinic date.¹⁸ A multivariate model to isolate predictors of failure to show up included age, gender, race, insurance status, local versus nonlocal residence, self-referral versus provider referral, and number of days from call to schedule an appointment to the new appointment date. Every 10 days between the call and the appointment date raised the no-show risk 32% (OR 1.32, 95% CI 1.14 to 1.53). (This finding inspired the Alabama group to fashion a program to get newly diagnosed people across the clinic threshold, as detailed below and in the interview with Michael Mugavero in this issue.)

Psychosocial, economic, and behavioral factors affecting entry to care

Broadly speaking, two groups contribute to sustained HIV incidence in the United States—gay and bisexual men and socially marginalized people who often belong to racial or ethnic minorities. Although these groups overlap, many gay and bisexual men have ready access to health care, harbor little suspicion of the health-care system, and understand what behaviors put them at risk of HIV infection. Most socially marginalized minorities, in contrast, have poor access to healthcare, may mistrust the healthcare system, and may not know or may ignore factors that raise their risk of HIV. If socially marginalized people do become infected, the same variables that put them at risk of HIV can keep them from seeking care. **Figure 2** outlines personal factors that affected entry to care in recent published reports.

■ **Race/ethnicity.** A comparison of two US HIV populations published in 2006 delineates the differences between the HIV-care haves and the

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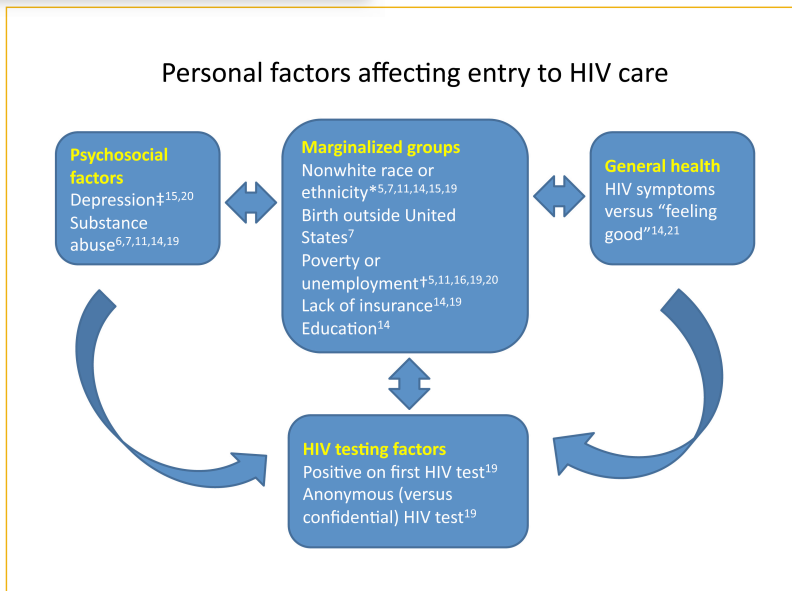


Figure 2. Factors that affect delayed entry to HIV care can be separated schematically and isolated in multivariate analyses. But the borders between individual risk factors and clusters of factors are blurred at best.

* Some studies determined that Hispanics have a lower risk of delayed access to care than other racial/ethnic groups.^{5,14}

† Some studies associate poverty with better access to care.^{5,11}

‡ Depression can heighten the risk of slow entry to care, and depressed people may be less likely to benefit from linkage intervention.¹⁵

have-nots.¹¹ The study focused on two groups: (1) 1286 people from 16 sites across the country who were interviewed in 2001-2002 in a study of underserved HIV-positive people targeted for supportive outreach services, and (2) 2267 people in the HIV Cost and Services Utilization Study (HCSUS), a probability sample of people already getting HIV care.

Compared with the HCSUS group, the outreach sample had a higher proportion of blacks (59% versus 32%, $P = 0.0001$), Spanish speakers (9% versus 2%, $P = 0.02$), people with an annual income under \$10,000 (75% versus 45%, P

$= 0.0001$), heroin or cocaine users (58% versus 47%, $P = 0.05$), and people who were unemployed, homeless, or had no insurance. Higher proportions of people in the outreach group had fewer than 2 ambulatory visits for HIV care (26% versus 16%, $P = 0.0001$) and had not started antiretroviral therapy (82% versus 58%, $P = 0.0001$). In the outreach group, heavy alcohol use ballooned the risk of low ambulatory clinic attendance almost 75% (AOR 1.74, 95% CI 1.23 to 2.45), and a CD4 count under 50 cells/mm³ raised that risk more than 50% (AOR 1.53, 95% CI 1.00 to 2.36).

The New York City study of 1928 people diagnosed with HIV in 2003 determined that non-white race or ethnicity upped the risk of delayed entry to care 80% (hazard ratio [HR] 1.8, 95% CI 1.5 to 2.0), birth outside the United States made delayed care 10% more likely (HR 1.1, 95% CI 1.0 to 1.2), and injection drug use raised the risk 30% (HR 1.3, 95% CI 1.1 to 1.5).⁷

Findings on whether Hispanic ethnicity, in itself, poses a hurdle to HIV care vary from study to study. CDC researchers interviewed 3942 HIV-positive people in 18 states from 2000 through 2004.¹⁹ About one quarter of this group (28%) did not start care for more than 3 months after they tested positive. Multivariate analysis accounting for numerous variables determined that Hispanics had a 33% higher risk of delayed entry (OR 1.33, 95% CI 1.05 to 1.69). The equally large, just-noted outreach-versus-HCSUS study¹¹ found that Hispanics ran more than a doubled risk of poor clinic attendance in the HCSUS sample (AOR 2.34, 95% CI 1.56 to 3.52), but being Hispanic did not correlate with inconsistent HIV care in the group of underserved people targeted for supportive outreach services (AOR 0.81, 95% CI 0.39 to 1.69). The Philadelphia study of 1266 people handed a positive HIV result found that Hispanic ethnicity predicted earlier HIV care (HR 1.39, 95% CI 1.05 to 1.84).⁵ In the 270-person ARTAS study, multivariate analysis linked Hispanic ethnicity (versus non-Hispanic black race) with a significantly higher likelihood of getting into care.¹⁴

The 2001-2003 randomized ARTAS study of 316 recently diagnosed people may help explain these between-study disparities in the impact of Hispanic ethnicity on entry to care.¹⁵ ARTAS investigators randomized these people to passive referral or a “strengths-based linkage

intervention” to ease entry into HIV primary care. The positive effect of the intervention was stronger in Hispanics than in other racial and ethnic groups combined (relative risk 1.53 versus 1.15), although that difference fell short of statistical significance ($P = 0.157$). This was a relatively small, 316-person study, and about 30% of participants were Hispanic; still, that result strongly hints that the Hispanics in this cohort (in Atlanta, Baltimore, Los Angeles, and Miami) responded better to linkage counseling than other groups did.

■ **Poverty and insurance.** No one needs a psychosociologic treatise to understand why poverty can keep recently diagnosed people out of the doctor’s office, especially in a country with a porous reimbursement scheme for poor people. But, as with ethnicity, the impact of poverty on getting into HIV care sometimes sorts oddly with intuition. The 18-state CDC study tied unemployment to a 23% higher risk of delayed entry to care (OR 1.23, 95% CI 1.04 to 1.45) in 3942 HIV-positive adults interviewed from 2000 through 2004.¹⁹ Unemployment nearly doubled the risk of poor linkage to care in a 180-person Houston study described below,²⁰ but that association did not reach statistical significance (AOR 1.78, 95% CI 0.92 to 3.43, $P = 0.09$). In a study of 365 hospitalized HIV-positive crack users, annual income under \$5000 hiked the odds of never being in care more than 8 times (AOR 8.17, 95% CI 3.35 to 19.94).¹⁶

The 3553-person outreach-versus-HCSUS study found that significantly more people in the underserved group targeted for HIV outreach than in the broadly based HCSUS sample had a yearly income under \$10,000 (75% versus 45%, $P = 0.0001$).¹¹ In the relatively wealthier HCSUS contingent, low income raised the risk

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of poor HIV clinic attendance 35% (AOR 1.35, 95% CI 1.04 to 1.75). But in the relatively poorer outreach cohort, low income *lowered* odds of bad clinic attendance more than 25% (AOR 0.73, 95% CI 0.56 to 0.96). And the Philadelphia study of 1266 people with HIV determined that living in a census tract with a high poverty rate improved chances of earlier entry to care (HR 1.68, 95% CI 1.22 to 2.30).⁵

Divergent findings on how poverty affects entry to care may be partly explained by whether low-income HIV-positive people benefit from good case management, programs that usher them into care, and decent health insurance. The CDC researchers who interviewed 3942 HIV-positive people in 18 states figured that those without insurance had a 20% higher risk of delayed entry to care (OR 1.20, 95% CI 1.03 to 1.41).¹⁹ And the 270-person ARTAS study linked public health insurance (versus no insurance) to a higher likelihood of seeing an HIV clinician.¹⁴

■ **Depression.** Getting diagnosed with HIV probably triggers depression, at least short-term depression, more often than not. The Steps Study, a prospective observational cohort study of people in Houston with newly diagnosed HIV, found that two thirds of 180 participants screened positive for depression on the 20-item CES-D scale.²⁰ Women made up one third of the study group, 51% were black, 39% Hispanic, and 10% non-Hispanic white. About half of these people had not finished high school, half had no job, and two thirds earned less than \$15,000 a year.

Multivariate analysis linked depression to female gender (AOR 5.71, 95% CI 1.76 to 18.5,

$P = 0.004$), any substance abuse in the last 6 months (AOR 3.93, 95% CI 1.49 to 10.3, $P = 0.009$), low self-reported access to medical care on a 6-point scale (AOR 4.69, 95% CI 1.48 to 14.9, $P = 0.009$), and low self-efficacy (belief in one's ability to do things for oneself) (AOR 3.05, 95% CI 1.22 to 7.63, $P = 0.03$).²⁰ Income over \$25,000 and a CD4 count of 200 to 350 cells/mm³ (versus under 200) independently lowered the odds of depression.

The Steps Study team defined successful linkage to HIV care as keeping an appointment in each of the first two 90-day periods after HIV diagnosis. Whereas 68% of people without depression entered care, 56% with depression got into care, a difference that fell short of statistical significance ($P = 0.11$). Multivariate analysis determined that depression doubled the risk of not starting HIV care, and that association nearly reached statistical significance (OR 2.00, 95% CI 0.96 to 4.14, $P = 0.06$).

These researchers proposed that “screening for depression should be undertaken at diagnosis of HIV seropositivity itself to identify persons at risk for poor follow-up and target them for unique interventions designed to bolster engagement in care.”²⁰ But depressed people may be less likely to benefit from targeted interventions, results of the ARTAS trial suggest.¹⁵ This study of 316 HIV-positive people randomized to passive referral to care or to a linkage intervention found that the linkage program worked better in people without depressive symptoms (relative risk 1.55 for people without depression versus 1.01 for people with depression, $P = 0.052$).¹⁵ In fact, people with depression were one of only four groups that did not benefit from a linkage program in this 26-group analysis (see “Holes in the health system” above).

■ **Substance abuse.** Interviewing 1038 HIV-positive people in two public hospitals in Miami and Atlanta, researchers found that 20% had never received HIV care, even though they knew they had HIV for more than 5 years.⁶ Four in 10 of these people had not had HIV care in more than 6 months. Multivariate analysis determined that using crack cocaine and heavy drinking raised the risk of (1) never having an HIV clinician, (2) high-risk sexual behavior, and (3) not receiving antiretroviral therapy. These investigators proposed that “inpatient interventions that link and retain HIV-positive persons in primary care services could prevent HIV transmission and unnecessary hospitalizations.”

The study that compared 1286 underserved HIV-positive people receiving an outreach intervention and 2267 HCSUS cohort members receiving HIV care found that heavy alcohol drinking independently raised the risk of inconsistent HIV clinic attendance in the outreach group (HR 1.74, 95% CI 1.23 to 2.45) but not in HCSUS (HR 1.00, 95% CI 0.73 to 1.37) ($P = 0.02$ for difference between outreach and HCSUS).¹¹

Injection drug use emerged as an independent predictor of delayed HIV care in at least three studies. CDC interviews of 3942 HIV-positive people in 18 states found that people infected while injecting drugs were 40% more likely than heterosexually infected people to delay HIV care for 3 months or more after diagnosis (OR 1.40, 95% CI 1.08 to 1.82).¹⁹ Using the same measure of delayed entry to care, the New York City Department of Health study of 1928 HIV-positive people figured that a history of injecting drugs (versus no history) raised the risk 30% (HR 1.3, 95% CI 1.1 to 1.5).⁷ The ARTAS study of 270 people who had never seen an HIV clinician (74%) or had seen a clinician only once

(26%) correlated never injecting drugs with a higher chance of seeing an HIV clinician within 6 months of enrolling in the study.¹⁴

■ **More factors.** The studies referenced above and others uncovered an array of other patient-related variables that stand between an HIV diagnosis and speedy care. One unsurprising but nonetheless noteworthy finding is that people who feel sick seek care, and people who don't, don't. Multivariate analysis in the 270-person ARTAS study determined that having three or more HIV-related symptoms independently raised chances of seeing an HIV provider within 6 months.¹⁴ And interviews with 130 HIV-positive people in Mississippi (81% black, 38% women) found that 47% who delayed HIV care more than 6 months listed “feeling good” as a reason, and 22% said “feeling good” was their main reason.²¹ Three quarters of the people in this study reported feeling denial about their HIV diagnosis, an attitude that would lend itself to delaying care.

The 3942-person CDC study found that first-time testers were 33% more likely to delay care (OR 1.33, 95% CI 1.13 to 1.56) than were people who had an earlier negative test.¹⁹ The CDC researchers cited a study that found gay men who got tested repeatedly for HIV had more positive health-related attitudes about testing,²² and the CDC team speculated that those same positive attitudes may apply to health care in general and thus favor starting care. The same CDC study found that anonymous HIV testing (rather than confidential testing) made delayed care almost 25% more likely (OR 1.24, 95% CI 1.03 to 1.51). The researchers suggested that “those diagnosed with HIV anonymously may wish to preserve their anonymity and simply avoid medical care for this reason.”¹⁹

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Finally, the 270-person ARTAS study figured that HIV-positive people with higher education were significantly more likely to begin care for their infection.¹⁴

Clinical impact of late entry to HIV care

No one needs vast experience with HIV infection—or much imagination—to grasp why delaying the first visit to an HIV clinic portends ominous clinical outcomes for people who test positive. Infection with a virus that relentlessly unpins the immune system kills most people, in time, unless they start taking drugs to pin down that virus. Probably for these reasons, research on the clinical impact of late entry to HIV care is sparse. But when hard numbers go lacking, modelers gleefully fill the breach. A modeling study that evaluated starting antiretrovirals late—at a CD4 count under 200 cells/mm³—figured that tardy treatment takes 24 years off a normal life span.²³

This novel analysis by modelers at Harvard and other centers tried to reckon life expectancy, compared with the general population, in four groups: (1) HIV-negative people with mortality risk profiles similar to people with HIV because of substance abuse and other high-risk behaviors, (2) HIV-positive people who begin antiretrovirals according to then-current guidelines, that is, when the CD4 count fell below 350 cells/mm³, and who go on to another regimen when one regimen fails, (3) HIV-positive people who do not start antiretrovirals till their CD4 count falls below 200 cells/mm³, and (4) people who do not start the next available antiretroviral regimen after failure of one regimen.

The investigators derived demographic data from HIV-positive people in several cohorts. At HIV seroconversion, this group averaged 33 years of age, had an average viral load of about 65,000 copies/mL, and averaged 534 CD4 cells/mm³. About half were black, 27% non-Hispanic white, and 21% Hispanic.

For 33-year-olds in the general US population, estimated life expectancy was an additional 42.9 years at the time of this study. For the HIV-negative group with a risk profile similar to US residents with HIV, life expectancy at age 33 would be only 34.6 years (**Figure 3**). In other words, compared with the general population, this “HIV-like” group would lose 8.3 years in life expectancy. For the HIV-positive group that starts antiretrovirals at the 350-cell threshold, life expectancy at age 33 would be 22.7 years, so they would lose an estimated 20.2 years compared with the general population.

For 33-year-old HIV-positive people who start antiretroviral therapy at a CD4 count between 50 and 199 cells/mm³, life expectancy would be only another 18.75 years, meaning they would lose 24.15 years compared with the general population, that is, 3.95 years more than the HIV-positive group that started antiretroviral therapy at the 350-cell cutoff. In this group that did not start antiretrovirals until their CD4 count lay between 50 and 199 cells/mm³, life expectancy would be 18.2 years for those who took four antiretroviral regimens before quitting, 17.0 years for those who took three regimens, 15.6 years for those who took two, and 13.7 years for those who took only one. To put it another way, dropping out of care earlier and earlier robs more and more years from an HIV-positive person's life.

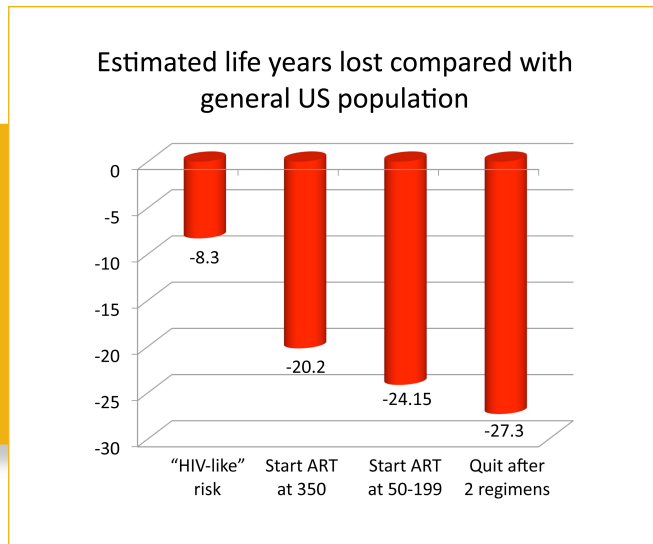


Figure 3. Compared with the general US population, HIV-negative people with a mortality risk profile similar to HIV-positive people (for example, because of substance abuse) would lose 8.3 years from the expected life of a 33-year-old (first bar), according to a modeling study.²³ HIV-positive people who start antiretroviral therapy (ART) at the 350 CD4 threshold and continue treatment with new regimens when one regimen fails would lose an estimated 20.2 years compared with 33-year-olds in the general population (second bar). HIV-positive people who do not start antiretroviral therapy until their CD4 count stands between 50 and 199 cells/mm³ would lose 24.15 years of life compared with 33-year-olds in the general population (third bar). And HIV-positive people who start treatment at 50 to 199 cells/mm³ but quit after two combinations fail would lose 27.3 years of life compared with the general population (fourth bar).

Of course much of the data summarized in the article on late HIV diagnosis in this issue of *RITA!* also suggest the clinical and monetary impact of delayed care after HIV diagnosis, because later diagnosis means later care.

Strategies to unstitch seams between HIV diagnosis and care

Indulgent readers will condone one more restatement of the obvious: HIV diagnosis earlier in the course of infection (the topic of the first article in this issue) will promote faster entry to care—or at least entry at a higher CD4 count and a less dire disease stage. But diagnosis with-

out linkage to care is almost pointless. And as Michael Mugavero and University of Alabama colleagues note, “although the importance of linkage to care is emphasized in the CDC guidelines, implementation has often focused on increasing the number of tests performed, with considerably less programmatic emphasis on linking patients to HIV care.”²²

In 2010 the US National HIV/AIDS Strategy outlined a plan to torque up access to care.²⁴ Though the goals are laudable, the recommended “action steps” are (in the nature of political manifestos) broad (**Table 2**). Still, the

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Table 2. US National HIV/AIDS Strategy to increase access to HIV care²⁴

Recommended action steps	Targets by 2015
<ol style="list-style-type: none"> 1. Establish a seamless system to immediately link people to continuous, coordinated quality care when they are diagnosed with HIV. 2. Take deliberate steps to increase the number and diversity of available providers of clinical care and related services for people living with HIV. 3. Support people living with HIV with co-occurring health conditions and those who have challenges meeting their basic needs, such as housing. 	<ol style="list-style-type: none"> 1. Increase the proportion of newly diagnosed patients linked to clinical care within 3 months of their HIV diagnosis from 65% to 85% (from 26,824 to 35,079 people). 2. Increase the proportion of Ryan White HIV/AIDS Program clients who are in care (at least 2 visits for routine HIV medical care in 12 months at least 3 months apart) from 73% to 80% (from 237,924 to 260,739 people in continuous care). 3. Increase the percentage of Ryan White HIV/AIDS Program clients with permanent housing from 82% to 86% (from 434,000 to 455,800 people).

document's first action step accurately embodies a key finding of research discussed above and below: smoothing out "seams" that hem the newly diagnosed from speedy care should be a priority. Studies show that intense case management after diagnosis, and/or housing testing and care services inside the same walls, can ease the way into care. But even targeted programs can yield disappointing results in recalcitrant populations.

Apparently only one randomized trial, by the CDC's Antiretroviral Treatment and Access Study (ARTAS), has assessed entry-to-care tactics.²⁵ The ARTAS team randomized just-diag-

nosed people to case management or passive referral standard-of-care (which seems standard when one considers the often lengthy lapse between a positive test and a handshake with an HIV clinician). This trial, published in 2005, involved 273 recently diagnosed people in Atlanta, Baltimore, Los Angeles, and Miami. The intervention included up to five contacts with a case manager over 90 days, while people in the passive referral group got only information about HIV and local care resources.

Significantly more people in the case-management group saw an HIV clinician at least once in 6 months (78% versus 60%, adjusted relative

risk 1.36, $P = 0.0005$), and at least twice in 12 months (64% versus 49%, adjusted relative risk 1.41, $P = 0.006$).²⁵ People older than 40, those who had not used crack recently, Hispanics, and people who enrolled in the trial within 6 months of HIV diagnosis were significantly more likely to have at least two HIV clinic visits. The CDC team estimated that this type of case management costs \$600 to \$1200 yearly—a pittance when weighed against the cost of delayed care. Although these results clearly demonstrate that one-on-one case management gets people into care more reliably than a stack of informational leaflets, the low 12-month visit rate in either study group suggests these people needed more help than they got.

Two other nonrandomized ARTAS studies evaluated case management and co-location, current jargon for having testing and treatment units under one roof. One of these later analyses focused on a larger group of 626 recently diagnosed people seen at 10 sites across the United States from 2004 through 2006.²⁶ All these people had up to five meetings with a linkage case manager over 90 days. In the first 6 months, 497 of the 626 study participants (79%) saw an HIV clinician, almost the same proportion as in the randomized trial.²⁵ People who had two or more case-management sessions and those seen at a site with testing and care under the same roof were significantly more likely to have an HIV office visit in 6 months. Other factors that favored linkage to care were age over 25, Hispanic ethnicity, stable housing, and no recent noninjection drug use. A separate analysis that used ARTAS data plus site visits and project director reports figured that sites with co-located testing and care had a substantially higher linkage rate than stand-alone sites, 87% versus 73%.²⁷

Four studies assessed how well outreach programs get underserved HIV-positive groups into care— injection drug users,^{28,29} nonwhites,^{29,30} and people with unstable housing.³¹ Street outreach for injection drug users²⁸ and peer-based outreach to people of color and injection drug users at 21 California sites (the California Bridge Project)²⁹ got only about half of study participants, at best, into care. Another California Bridge Project study focused on 325 out-of-treatment HIV-positive people who averaged 1.5 years since HIV diagnosis and their first meeting with project staff.³⁰ Almost three quarters of these people were nonwhite, and half were men who have sex with men. Case workers managed to link only 29% of this group to care—after an average 15.4 client contacts. Although these outreach programs linked half or fewer people to HIV care, the success rate surely reflects the hard-to-reach populations that the programs targeted.

An outreach program in New York City targeted 161 HIV-positive residents of single-occupancy hotels, 95% of whom were minorities and 59% of whom were active drug users.³¹ Ninety-five study participants were assessed before receiving the intervention, while 66 were assessed after receiving the intervention. These people had better baseline access to care than the groups in the studies summarized above.²⁸⁻³⁰ Three quarters of the pre-intervention group and 91% of the postintervention group already had a regular health care provider.

In the pre-intervention approach, an outreach worker went door-to-door in eight single-occupancy hotels and asked residents if they needed services and wanted to join a harm-reduction program. The intervention consisted of adding

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a physician to the door-to-door outreach team and asking residents if they wanted to see a physician right now. Comparing data from pre-intervention and postintervention interviews, multivariate analysis that accounted for drug use, HIV severity, and other factors determined that the intervention independently raised chances of having a regular provider (OR 5.3, $P = 0.02$), taking antiretrovirals (OR 5.7, $P = 0.02$), and having a better perception of quality of care (OR 4.9, $P = 0.003$).

Besides case management, outreach, and collocation of testing and care services, a few studies have pinpointed specific tactics that may cut the time between HIV diagnosis and care (**Table 3**). The already-discussed University of Alabama HIV clinic study found that every 10 days between the call to make a first clinic appointment and the appointment date magnified the no-show risk about 30%.¹⁸ Other research shows the importance of having appointment times convenient for patients and having providers who speak the patient's language.^{32,33} In a review article on improving US women's access to care, Mariam Aziz and Kimberly Smith of Chicago's Rush University Medical Center stressed the need to create a "woman-friendly environment" that offers child care and access to "case management, social workers, and gynecologic care, at a minimum."³⁴

After Michael Mugavero and University of Alabama colleagues figured out why HIV-positive people failed to show up for their first HIV clinic appointment,¹⁸ they devised a program, Project CONNECT, to help solve the problem.³⁵ Newly diagnosed people are scheduled for a clinic orientation visit within 5 days of their first call for an appointment (see **Figure 1** in the Mugavero interview). That visit includes a semistructured interview, a psychosocial questionnaire, baseline lab tests, and (for the uninsured) a visit with a social worker. Patients needing substance abuse or mental health services get a prompt referral to appropriate services. Because the clinician has lab results and other data at the first patient encounter, care can begin immediately. During the first year that Project CONNECT was in place, the clinic's no-show rate dropped from 31% to 18% ($P < 0.01$).² CONNECT cut the risk of failure to establish HIV care almost 50% (OR 0.54, 95% CI 0.38 to 0.76).

San Francisco General Hospital (SFGH), which cares for large populations of gay men and poor, homeless, or uninsured people, created the Positive Health Access to Services and Treatment (PHAST) system to get newly diagnosed people into care.^{36,37} All SFGH care settings use rapid HIV testing and a central diagnostic lab that pages positive results to a PHAST worker, who meets patients when they get a positive result.

Table 3. Getting newly diagnosed people into HIV care: strategies that work

- Active case management rather than passive referral upon HIV diagnosis^{25-27,35-37}
- Housing HIV testing services in the same building as an HIV primary care clinic^{26,27}
- Street and community outreach to find HIV-positive people not in care²⁸⁻³¹
- Shorter time between call for first appointment and first appointment¹⁸

The PHAST team member provides intensive on-the-spot support and education, schedules confirmatory testing, and performs clinic intake including CD4 count, viral load, and resistance testing. PHAST also helps newly diagnosed people with insurance applications and provides appointment reminders and primary care until the patient is transferred to a permanent HIV provider.

Sobering numbers on staying in care

After HIV diagnosis and linkage to care, the third leg in the HIV-health tripod is staying in care, or retention. Using data from the CDC and other sources, researchers estimated that 79% of the 1.1 million HIV-positive people in the United States get diagnosed, 59% enter care, and only 40% stay in care.³⁸ (See **Figure 1** in the article “Late HIV diagnosis.”) Looking at specific HIV populations, other investigators usually make similarly depressing estimates of retention in care.

Meta-analysis of HIV linkage and retention studies with data from May 1995 through 2009 figured that, of 75,655 people who entered care, only 59% kept multiple HIV visits averaged across assessment intervals ranging from 6 months to 3 to 5 years.³⁹ A British study of 16,595 people in HIV care determined that 44% did not have a CD4 count for a year or more, and 40% of that group fell out of care for the duration of follow-up.⁴⁰ A 12,304-person EuroSIDA analysis published in 2008 defined loss to follow-up as no clinic visit, CD4 count, or viral load assay after January 1, 2006; the researchers counted 2712 people (22%) who met those criteria.⁴¹ Recruitment of the analyzed cohorts began in May 1994 and ended in December 2005. In contrast to these findings, another prospective

cohort, the French Hospital Database on HIV, found in 2006 that only 2950 of 34,835 people (8.5%) did not have a medical visit for at least 12 months after their last visit in 1999.⁴² But loss to follow-up was 16.8% among people diagnosed with HIV in the past year.

Retrospective analysis of 2619 male US veterans who started antiretroviral therapy after January 1, 1998 determined that 36% went at least 3 months without seeing their HIV clinician in the first year of therapy.⁴³ Among 1636 people who entered the University of North Carolina Center for AIDS Research prospective clinical cohort from January 2001 through January 2008, 414 (25%) dropped out of care, defined as missing appointments for 18 months.⁴⁴ A New York City study of 842 people diagnosed with HIV from July 1 to September 30, 2005 found that 650 (77%) started care within 3 months.⁴⁵ Of those, only 45% maintained regular care, defined as at least one clinic visit every 6 months.

Why people with HIV drop out of care

Many variables that shorten the odds of starting HIV care also explain why people later quit. Whether the study group lives in the United States or Western Europe, factors that make poor retention more likely often include younger age, minority or immigrant status, substance use, and a very low CD4 count (**Figure 4**). People with AIDS, in contrast, seem more likely to keep appointments than people without AIDS.

To analyze predictors of retention in HIV care, *RITA!* sifted results of 9 studies that used multivariate analysis to pinpoint retention predictors. The four biggest studies scrutinized large cohorts—34,835 people in the French Hospital Database on HIV,⁴² 12,304 in EuroSIDA⁴¹ 2619

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Predictors of dropping out of care in nine studies

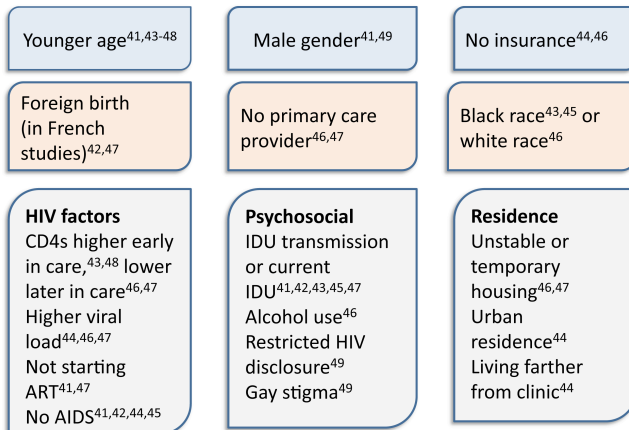


Figure 4. An array of factors independently predicted dropping out of care in nine US and European studies. From study to study, the most consistent predictors were younger age, not having AIDS, injection drug use, and numerous factors indicating social marginalization. The appendix following the references in this article spells out results of these studies.

men cared for at US Veterans Affairs (VA) centers,⁴³ and 2411 or 1924 HIV-positive women (depending on the analysis) in the six-site US Women's Interagency HIV Study (WIHS).⁴⁶ (WIHS kept tabs on cohort visits, not on primary care HIV visits.) Smaller populations included 1636 people seen at the University of North Carolina HIV clinic,⁴⁴ 1007 patients in five French HIV clinics,⁴⁷ 650 people in New York City,⁴⁵ 567 people at the University of Alabama HIV clinic,⁴⁸ and 398 people in Los Angeles clinics.⁴⁹ The VA study differed from the others in the stringency of its definition of poor retention—missing a clinic visit in any one of four quarters in the first year of antiretroviral therapy.⁴³ The appendix following the references to this article details how each of these studies defined retention and outlines key results.

Younger age consistently boosted the risk of poor retention in the VA study, WIHS, and the clinic-based studies,⁴³⁻⁴⁸ while older age favored

good retention in EuroSIDA.⁴¹ EuroSIDA linked female gender to better retention,⁴¹ while the Los Angeles study found that Latina and African-American women were more likely to keep clinic appointments than Latino or African-American gay men.⁴⁹ The all-men VA study determined that black veterans ran a one-third higher risk of poor retention than white veterans.⁴³

How HIV disease status affects retention seems a little trickier to reckon, but in the end none of these disease status results defy logic. First, people with an AIDS diagnosis were more likely to see their HIV physician regularly in the French Hospital Database,⁴² EuroSIDA,⁴¹ and the University of North Carolina clinic;⁴⁴ this consistent result reflects the likelihood that people who have an AIDS disease or had one earlier want their AIDS treated right away or want to avoid repeating the experience. Conversely, the New York City study identified early (non-AIDS) HIV infection as a predictor of poor retention.⁴⁵

People with higher viral loads proved more likely to drop out of care at the University of North Carolina,⁴⁴ in WIHS,⁴⁶ and in the French clinic study.⁴⁷ Although those findings at first seem at odds with the AIDS results, it makes sense that people with higher viral loads are dropout risks because high loads often reflect poor antiretroviral adherence; and people with poor antiretroviral adherence are candidates for poor appointment adherence. High loads may also indicate lack of antiretroviral therapy, and taking antiretrovirals correlates with good retention, as discussed below.

WIHS⁴⁶ and the five French clinics⁴⁷ linked a lower CD4 count to poor clinic attendance, while EuroSIDA⁴¹ and the Los Angeles study⁴⁹ figured a higher CD4 count favored good clinic attendance. The VA and University of Alabama studies found that a higher initial CD4 count predicted poor retention,^{43,48} while the French clinic study found that a lower initial CD4 count predicted good retention.⁴⁷ What do these mixed results mean? There's no way to know for sure because studies that demonstrate associations do not establish the direction of causality. But there's plenty of room for speculation:

A very low CD4 count may signal advanced HIV disease and imminent death, which would tend to keep people out of the clinic. Indeed, some people listed as "lost to follow-up" may have died. A higher CD4 count can reflect good adherence to antiretrovirals and to care in general and thus explain good clinic attendance. On the other hand, a high CD4 count when first entering care probably reflects asymptomatic disease, and people with no symptoms have less motivation to keep clinic appointments. The timing of the CD4 measurement is critical, as the five-

clinic French study showed by evaluating CD4 count two ways.⁴⁷ In this 1007-person study, a low initial CD4 count favored good retention,⁴⁷ probably for the same reason that an AIDS diagnosis favors good retention: sick people who just learned they have HIV want to get care. The same French study found that a lower CD4 count during care made poor retention more likely,⁴⁷ perhaps because people whose CD4 count stays low despite being in care are not taking antiretrovirals and are missing appointments, or they are getting too sick to come to clinic.

The studies that isolated antiretroviral therapy as a retention predictor revealed the two sides of the treatment coin. EuroSIDA members who had begun antiretroviral therapy were more likely to stay in care,⁴¹ while people not taking antiretrovirals in the five French clinics were more likely to drop out.⁴⁷ One could theorize endlessly on what is cause and what is effect in these associations, but few would disagree with one interpretation: getting patients to the point where they can start antiretrovirals helps keep them from turning truant.

Minority status, figured different ways, heightens the risk of poor clinic attendance. In both French studies,^{42,47} being born outside of France raised the risk of poor retention in care, and black race made poor retention more likely in the VA survey⁴³ and the New York City study.⁴⁵ But in the WIHS study of US women, white women were more likely than black women to miss WIHS study visits 7 through 10.⁴⁶ Why white race correlated with poor study attendance in WIHS is not clear; many women in this six-center cohort are socially marginalized regardless of race or ethnicity.

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People without a primary care provider ran a higher risk of missing cohort appointments 7 through 10 in WIHS⁴⁶ and of dropping out of care in the French clinic study.⁴⁷ Women with no health insurance or with temporary housing were more likely to miss appointments in WIHS,⁴⁶ while having no phone number (a surrogate for poverty or transience) in the French study predicted dropping out of care.⁴⁷ Having insurance favored good retention at the University of North Carolina HIV clinic.⁴⁴ Substance abuse upped the odds of poor retention in WIHS⁴⁶ and the University of Alabama clinic,⁴⁸ while moderate (but not heavy) alcohol drinking made poor retention more likely in WIHS.⁴⁶ The Los Angeles analysis of Hispanic or black women or gay men was the only study that weighed the impact of HIV disclosure status.⁴⁹ People who told more “network members” they had HIV were more likely to stay in care. In the same study, Latino gays who felt more gay stigma made fewer clinic visits. In the VA study, men with a chronic nonviral disease such as diabetes, hypertension, or ischemic heart disease had about a 20% lower risk of poor retention (OR 0.81, 95% CI 0.66 to 0.99).⁴³

Erratic appointment keeping and death

HIV clinicians need no instruction on the baleful consequences of missing appointments or falling out of care completely. But it is instructive to see how consistently poor retention predicts death in diverse HIV populations studied in the past 5 years.

The largest such study involves 2619 HIV-positive men diagnosed in Veterans Affairs hospitals or clinics in 1997 and 1998.⁵⁰ All these men started antiretroviral therapy after January 1,

1997, saw an HIV clinician at least once after starting, and survived at least 1 year. Median pretreatment CD4 count stood at 228 cells/mm³, median viral load measured about 38,000 copies/mL, and follow-up averaged more than 4 years. During years in which men made at least one clinic visit, 36% had visits in fewer than four quarters and 16% died during follow-up. Multivariate regression analysis determined that, compared with men who made a clinic visit in all four quarters, those who made visits in three, two, or one quarter all had a higher risk of dying during follow-up:

Hazard ratio for death compared with HIV clinic visits in 4 quarters per year:

- Visits in 3 quarters: HR 1.42 (95% CI 1.11 to 1.83), $P < 0.01$
- Visits in 2 quarters: HR 1.67 (95% CI 1.24 to 2.25), $P < 0.001$
- Visit in 1 quarter: HR 1.95 (95% CI 1.37 to 2.78), $P < 0.001$

A retrospective statewide study in South Carolina involved 2197 HIV-positive people at least 13 years olds who were diagnosed with HIV from 2004 through 2007 and entered care.⁵¹ The investigators defined retention as optimal if a person visited a clinic once every 6 months in the first 2 years of care, suboptimal if they made visits in three of four 6-month intervals, sporadic if they made visits in two of four intervals, and dropout if they made no visits. Half of the study group failed to get to the clinic at least once every 6 months in the 2 years after diagnosis. Sporadic retention almost tripled the risk of death during follow-up (AHR 2.91, 95% CI 1.54 to 5.50) and dropping out quadrupled the risk (AHR 4.00, 95% CI 1.50 to 10.65).

University of Alabama researchers retrospectively analyzed mortality in 543 HIV-positive people who started outpatient care between January 2000 and December 2005, with follow-up through August 1, 2007.⁵² Most people, 60%, missed at least one scheduled appointment during the first year of care. Death rates were 1.0 per 100 person-years among people who kept all clinic appointments in the first year of care and 2.3 deaths per 100 person-years among people who missed one or more visits ($P = 0.02$). Compared with people who always kept appointments, those who missed visits ran a tripled risk of death during follow-up (HR 2.90, 95% CI 1.28 to 6.56).

Even when people who drop out of care return, the higher death risk persists, according to results of a study in northern France.⁵³ From 1997 through 2006, researchers at 5 clinics around Lille classified 135 of 1007 HIV patients (13%) as lost to follow-up, defined as not coming to the clinic for 12 months, not known to be in care elsewhere, and not known to have died. Seventy-four of the 135 dropouts (55%) returned to care after a median of 19 months, and 33 of those 74 (45%) had a CD4 count below 200 cells/mm³ and/or AIDS when they came back. Compared with clinic patients who never dropped out, those returning to care were more likely to be younger (median 31 versus 35 years, $P < 0.001$) and injection drug users (12% versus 2.6%, $P < 0.001$), and less likely to have an AIDS illness upon entering care (11% versus 20%, $P = 0.01$). An analysis that adjusted for CD4 count and AIDS diagnosis at enrollment figured that people who returned to care after loss to follow-up had a 5 times higher risk of dying than people who never left care (OR 5.14, 95% CI 2.11 to 12.54).

Strategies to promote steady care: what works?

Although strategies to promote retention in care have not been studied as closely as antiretroviral adherence tactics, researchers have proposed and tested an armful of retention programs. Harvard's Elizabeth Horstmann and coworkers at other centers tabulated and reviewed eight such blueprints,⁵⁴ and others are easy to find. But perhaps the most practical overall advice comes from Thomas Giordano, who studies retention (and other things) at Houston's Baylor College of Medicine and Veterans Affairs Medical Center. Giordano concludes a list of 10 retention tips for HIV clinicians with these no-nonsense points:⁵⁵

Patients know they should be in care:

- Reminders are likely not enough.
- Admonishments or encouragements will not work.
- Problem solve with your patients just as you would for adherence to medications.

The intervention studies reviewed by Horstmann⁵⁶⁻⁶³ plus additional studies identified by *RITA!*,⁶⁴⁻⁶⁸ usually involve some type of case management, outreach, "system navigator," or ancillary services (**Figure 5**). Tactics range from the simple (answering medical questions^{59,64}) to the complex (planning and launching a "social marketing campaign"⁶⁴). Horstmann's recent review of retention strategy studies⁵⁴ found that facets of all such programs⁵⁶⁻⁶³ improved appointment keeping by people with HIV. All of the additional retention strategy studies tracked down by *RITA!*,⁶⁴⁻⁶⁸ which include programs for women, youth, and children, found that at least some components of these programs helped keep people in care.

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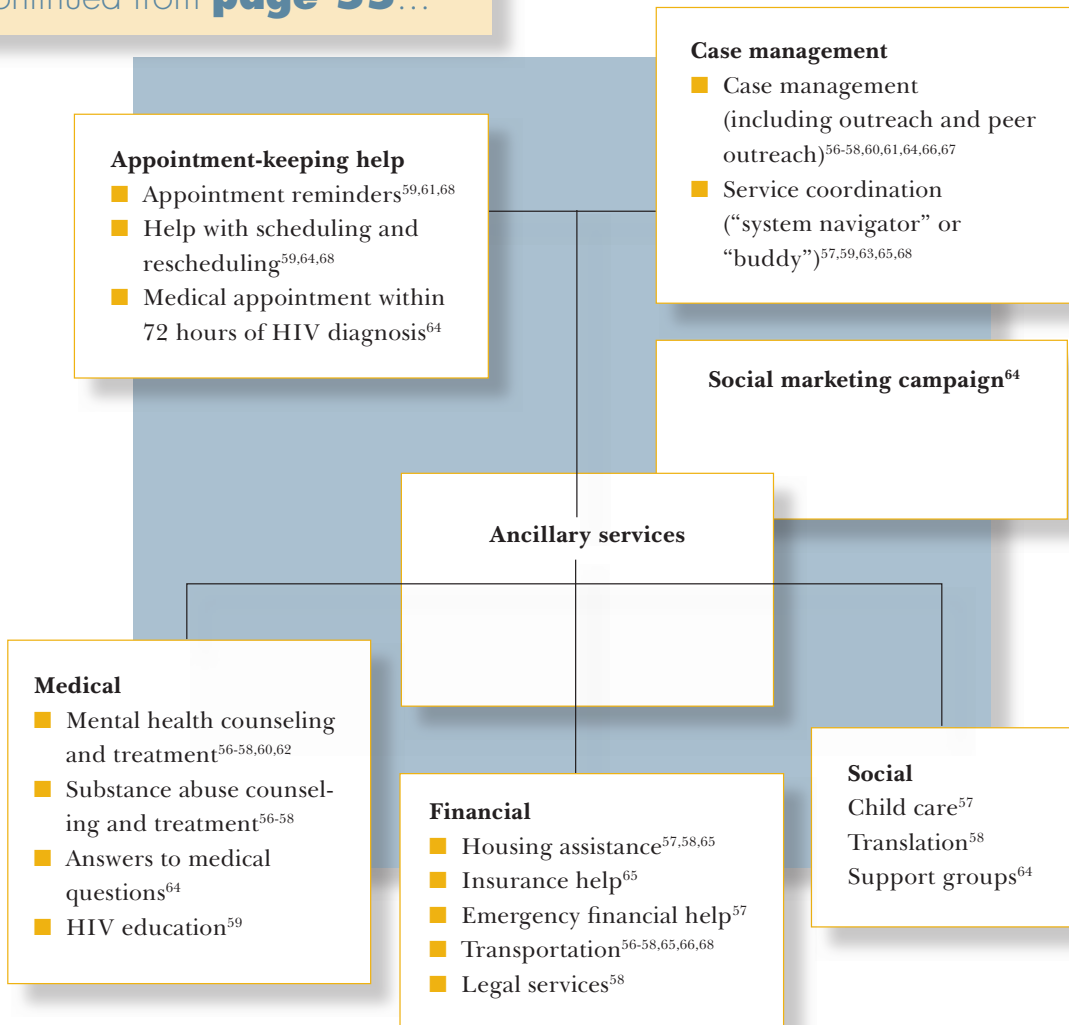


Figure 5. Several clusters of retention strategies have proved at least partly effective in people with HIV.

The bottom line from all this work appears to be that doing something is better than doing nothing. But how much can any busy HIV practice do to keep patients coming back? Beyond broad programs such as case management, certain specific services worked across diverse populations:

- Clinic appointment reminders^{59,61,68}
- Help with appointment scheduling and rescheduling^{59,61,64,68}
- Service coordination via a “system navigator” or “buddy”^{57,59,63,65,68}
- Mental health counseling and treatment^{56-58,60,62}
- Substance abuse counseling and treatment⁵⁶⁻⁵⁸
- Housing assistance^{57,58,65}
- Food and nutrition support^{57-59,65,68}
- Transportation^{56-58,65,66,68}

Some programs incorporate services that make sense but may be too costly for many clinics, such as child care,⁵⁷ translation services,⁵⁸ insurance help,⁶⁵ legal assistance,⁵⁸ and emergency financial aid.⁵⁷ Just as quickly making a first HIV clinic appointment improved entry to care in a study reviewed above,¹⁸ making the first medical appointment within 72 hours of HIV diagnosis improved retention in a University of North Carolina study.⁶⁴

Giving each HIV patient a “system navigator” or “buddy” has become a popular approach to improving retention, at least in studies of ways to bolster appointment keeping.^{57,59,63,65} This personal ombudsman, often a peer, helps patients pick their way through an increasingly brambly sociomedicolegal thicket that can baffle even the most-motivated person. “Navigator” is not just a trendy rubric for “case manager” since the navigator typically joins the patient on clinic visits and works with the patient day to day. “Patient navigators,” explains the University of Alabama’s Michael Mugavero, “are often HIV-infected peers or near-peers who share similar cultural and socioeconomic backgrounds as the patient, often playing a distinct and complementary role to case managers and other supportive service providers.”² However, the potential benefit of system navigators remains to be studied rigorously in a randomized trial.

In addition to the problem-solving advice listed at the beginning of this section, Thomas Giordano offers the following practical pointers on keeping HIV patients in care:⁵⁵

- Track no-show and out-of-care rates.
- Examine your processes: Bringing patients back is much more difficult once they are out of care completely.

- Work with emergency room and inpatient services, community-based organizations, public health agencies, jails/prisons, and other Ryan White providers to identify patients poorly retained in care and to build or strengthen re-linkage processes.
- Build or strengthen outreach or peer navigator programs.
- Work with the resources you have: Spread the word about the importance of retention; have staff advocate with patients for retention.
- Improve the customer’s experience.
- Minimize unmet needs: Strengthen substance use, mental health, case management, and social services.
- Minimize time between appointment making and appointment date.
- Pilot wider appointment availability, open access.

Summary points on linkage and retention

Linkage

- Two years after getting a positive HIV test, one third of Americans still have not had a CD4 count, according to the CDC.¹
- Health system problems that delay entry to care include separate HIV testing and care facilities, passive referral instead of active case management, and longer time between referral and the first scheduled visit.^{2,18}
- Two HIV testing factors heighten the risk of delayed entry to care: testing positive the first time tested, and anonymous versus confidential HIV testing.¹⁹
- The only randomized trial of methods to improve linkage to care confirmed the superiority of case management over passive referral after HIV diagnosis.²⁵

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■ Focused linkage programs at the University of Alabama³⁵ and San Francisco General Hospital^{36,37} have had some success.

Retention

■ Of the 1.1 million HIV-positive people in the United States, perhaps only 40% get diagnosed, enter care, and stay in care.³⁸

■ Across nine retention studies, factors that most consistently predicted dropping out of care were younger age, minority or immigrant status, substance use, and a low CD4 count.

■ Not taking antiretroviral therapy boosted the risk of dropping out of care in two large cohort studies.^{41,47}

■ Four studies concurred in finding that dropping out of HIV care, or dropping out and returning after a year, raised the risk of death.⁵⁰⁻⁵³

■ Programs that promote good retention include case management, “system navigators,” and ancillary care such as mental health and substance abuse services.⁵⁶⁻⁶⁸

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Appendix:

Nine studies to pinpoint predictors of poor retention in care

RITA! found nine published studies that use multivariate analysis to identify independent predictors of retention in HIV care. Overall results are described and analyzed above under the subhead "Why people with HIV drop out of care." Definitions of retention and study details follow.

The French Hospital Database on HIV offers the biggest retention-in-care analysis, embracing 34,835 HIV-positive people enrolled since 1999.⁴² The investigators defined loss to follow-up as not being seen for at least 12 months after a visit in 1999. Loss to follow-up was more frequent among people diagnosed in the past year than in those diagnosed more than 1 year ago (16.8% versus 7.1%). Among people diagnosed in the past year, loss to follow-up was 40% less likely among those infected during sex between men than in other transmission groups (OR 0.60, 95% CI 0.5 to 0.7) and 50% less likely in people with AIDS (OR 0.5, 95% CI 0.4 to 0.6). Immigrants were 30% more likely to drop out of care than natives (OR 1.3, 95% CI 1.0 to 1.5). Overall loss to follow-up proved 20% more likely among injection drug users than among men who have sex with men (OR 1.2, 95% CI 1.1 to 1.4).

A 12,304-person EuroSIDA analysis published in 2008 defined loss to follow-up as no follow-up visit, CD4 count, or viral load after January 1, 2006.⁴¹ Women were almost 10% less likely to fall out of care than men (incidence rate ratio [IRR] 0.91, 95% CI 0.83 to 1.00, $P = 0.039$), while every 10 years of age made falling out of care almost 20% less likely (IRR 0.82, 95% CI 0.78 to 0.85, $P < 0.0001$). Every 2 times higher CD4 count lowered the chance of loss to follow-up 7% (IRR 0.93, 95% CI 0.91 to 0.96, $P < 0.0001$), and starting combination antiretroviral therapy lowered the risk more than 30% (IRR 0.69, 95% CI 0.63 to 0.76, $P < 0.0001$). Having AIDS made loss to follow-up about 15% less likely (IRR

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0.84, 95% CI 0.77 to 0.92, $P < 0.0001$). Getting infected by injecting drugs rather than via other routes upped the risk of loss to follow-up about 35% (IRR 1.36, 95% CI 1.22 to 1.52, $P < 0.0001$).

The biggest US study to probe for retention variables involved 2619 male US veterans who started therapy after January 1, 1998.⁴³ This study differs from others reviewed here not only in its all-male all-veteran population (62% black or Hispanic, 22.5% with HCV, 28% with “socioeconomic instability”), but also in the stringent definition of poor retention in care—missing a primary care visit in any one of four quarters during the first year of antiretroviral therapy. Multivariate analysis isolated several predictors of poor retention: younger age (OR 1.41, 95% CI 1.13 to 1.75 for 40 to 49 versus 50 or older; higher odds ratios for 30 to 39 and 20 to 29 versus 50 or older), black versus white race (OR 1.34, 95% CI 1.11 to 1.62), CD4 count above 350 cells/mm³ versus under 200 cells/mm³ (OR 1.25, 95% CI 1.02 to 1.52), hepatitis C infection (OR 1.32, 95% CI 1.06 to 1.64), and illicit drug use (OR 1.42, 95% CI 1.08 to 1.87). Having a chronic medical condition other than HIV or HCV (such as diabetes, hypertension, or ischemic heart disease) lowered the risk of poor retention (OR 0.81, 95% CI 0.66 to 0.99).

Another large US analysis of retention in care involved more than 2000 HIV-positive women in the Women’s Inter-agency HIV Study (WIHS), which regularly monitors HIV-positive and at-risk women at six centers.⁴⁶ This analysis identified factors that predict keeping WIHS visits, not visits to these women’s primary care or HIV clinicians. Still, the study offers useful insights into why poor minority women, who make up the bulk of WIHS enrollees and reflect the US female HIV population, have trouble keeping medical appointments.

WIHS researchers determined reasons why women missed cohort visits 2 and 3 or cohort visits 7 through 10. Among 2411 HIV-positive women in the visit 2-3 analysis, factors that independently predicted nonattendance were temporary housing (OR 2.80, 95% CI 1.74 to 4.50, $P < 0.001$), moderate alcohol consumption (OR 1.46 for 1 to 13 drinks weekly versus none, 95% CI 1.04 to 2.07, $P = 0.03$), use of crack, cocaine, or heroin (OR 2.56, 95% CI 1.43 to 4.57, $P < 0.01$), lower CD4 count (OR 0.84 for each log₂ higher CD4 count, 95% CI 0.74 to 0.95 $P < 0.01$), higher viral load (OR 1.37 for each log₁₀ higher viral load, 95% CI 1.11 to 1.71, $P < 0.01$), and having a primary care provider (OR 2.14, 95% CI 1.30 to 3.52, $P < 0.01$). The last finding runs counter to results when the WIHS team analyzed visits 7 through 10.

Among 1924 women, missing WIHS visits 7 through 10 was more likely with younger age (OR 0.78 for each added 10 years of age, 95% CI 0.68 to 0.89, $P < 0.001$), white versus black race (OR 1.58, 95% CI 1.19 to 2.10, $P < 0.001$), not having a primary care provider (OR 0.77 for having a provider, 95% CI 0.60 to 0.99, $P = 0.04$), not having health insurance (OR 0.74 for having insurance, 95% CI 0.56 to 0.96, $P = 0.03$), higher viral load (OR 1.16 for each log₁₀ higher, 95% CI 1.04 to 1.30, $P < 0.001$), and nonattendance at a previous visit (OR range 3.31 to 30.7 depending on missed visit sequence, $P < 0.001$).

University of North Carolina (UNC) investigators assessed retention of 1636 people in the UNC Center for AIDS Research prospective clinical cohort after enrollment between January 1, 2001 and January 1, 2008.⁴⁴ Most of these people (58%) were African American, and 32% were women. Defining dropout as failing to keep clinic visits for 18 months, the UNC researchers found that every 10 years of age raised chances of study retention 12% (AHR 1.12, 95% CI 1.00 to 1.25), having private insurance (versus none or “other”) raised retention chances almost 50% (AHR 1.46, 95% CI 1.14 to 1.86), and having public insurance (versus none or “other”) raised chances about 30% (AHR 1.31, 95% CI 1.03 to 1.66). Having AIDS made retention 30% more likely (AHR 1.30, 95% CI 1.03 to 1.64), but having a detectable viral load almost halved chances of staying in care (AHR 0.52, 95% CI 0.40 to 0.66, for more than 10,000 copies/mL versus under 400 copies/mL; AHR 0.58, 95% CI 0.45 to 0.75, for 400 to 10,000 copies/mL versus under 400 copies/mL). Living in an urban area made retention 30% less likely (AHR 0.70, 95% CI 0.55 to 0.88), and living farther from the clinic cut chances about 25% for every 50 miles (AHR 0.74, 95% CI 0.66 to 0.84).

A study of 1007 HIV-positive people in care from January 1997 to December 2006 in five French clinics identified risk factors for loss to follow-up, first, when people joined the study group and, second, during follow-up.⁴⁷ Baseline variables that raised the risk of dropping out of care were age under 30 versus over 40 (HR 1.66, 95% CI 1.04 to 2.64), trans-

mission by injection drug use rather than sex between men (HR 5.26, 95% CI 2.90 to 9.52), no phone number provided (HR 5.4, 95% CI 3.6 to 8.2), no primary care physician (HR 2.10, 95% CI 1.25 to 3.52), and sub-Saharan African origin (HR 2.09, 95% CI 1.36 to 3.22). Baseline variables that lowered the risk of loss to follow-up were a CD4 count below 200 cells/mm³ versus over 349 cells/mm³ (HR 0.49, 95% CI 0.32 to 0.76) and a CD4 count of 200 to 349 cells/mm³ versus over 349 cells/mm³ (HR 0.63, 95% CI 0.41 to 0.98). During follow-up, chances of falling out of care were higher with a most recent CD4 count under 200 cells/mm³ (HR 2.06, 95% CI 1.16 to 3.66), not taking antiretroviral therapy (HR 4.20, 95% CI 2.66 to 6.61), and taking antiretrovirals but having a detectable viral load (HR 1.92, 95% CI 1.19 to 3.01).

A New York City study of 650 people diagnosed with HIV in 2005 and starting care within 3 months defined regular care as 1 or more clinic visit every 6 months and retention in care as the last visit within 6 months of the end of analysis on June 30, 2009.⁴⁵ Variables that raised the odds of not having regular care were age 13 to 24 versus 50 or over (AOR 3.0, 95% CI 1.5 to 6.0), black race (AOR 2.0, 95% CI 1.4 to 2.8), eligibility for antiretroviral therapy (AOR 1.5, 95% CI 1.1 to 2.2), and injection drug use (AOR 2.7, 95% CI 1.0 to 7.1). Factors that made quitting care more likely were age 13 to 24 versus 50 or over (AHR 1.9, 95% CI 1.1 to 3.4), nonhospital site of care (AHR 1.4, 95% CI 1.0 and 2.0), and early-stage (non-AIDS) disease (AHR 1.4, 95% CI 1.0 to 2.0).

The University of Alabama group studied 567 people starting outpatient care at their clinic between January 2000 and December 2005.⁴⁸ The investigators defined retention in care as the number of 6-month blocks during which a person attended at least one clinic visit over the 2 years after the first outpatient HIV primary care visit (range 1 to 4). Younger age independently predicted worse retention in the first 2 years of care (OR 0.7 per 10 years older, 95% CI 0.57 to 0.86), as did higher initial CD4 count (OR 2.65, 95% CI 1.6 to 4.38 for 200-349 cells/mm³ versus under 200 cells/mm³; OR 2.48, 95% CI 1.6 to 3.86, for 350 cells/mm³ or higher versus under 200 cells/mm³). Substance abuse also raised the risk of poor retention (OR 1.67, 95% CI 1.02 to 2.71), but having an affective mental health disorder cut the risk of poor retention (OR 0.45, 95% CI 0.31 to 0.67). To explain the last finding, the investigators speculated that people with diagnosed mental health problems may be getting treatment or special attention for that problem, whereas people with undiagnosed mental health problems would not be getting special care and thus would be more likely to miss clinic appointments.

A study of 398 HIV-positive people in Los Angeles included roughly equivalent proportions of Latino and African-American gay or bisexual men and Latina and African-American women.⁴⁹ They completed a 45-minute survey on demographics, HIV status disclosure, HIV-specific and general stress, gay- and HIV-related stigma, social support, and other health variables. The investigators rated 307 people as retained in care because they had 2 or more primary care visits in the 6 months before the interview and 91 people as not retained in care because they had 0 or 1 visit in the 6 months before the interview.

In the whole study group, HIV status disclosure to more personal network members was the primary predictor of good retention (OR 1.3, 95% CI 1.1 to 1.5). Among Latino gay men, gay stigma lowered chances of retention 10% (OR 0.9, 95% CI 0.8 to 0.9). Among people who disclosed their HIV status to one or more network members, predictors of retention in care were gender (OR 1.8 for women versus gay men, 95% CI 1.1 to 3.1) and disclosure of HIV status to more network members (OR 1.5, 95% CI 1.1 to 1.9). Among Latino gays who disclosed their HIV status, those with higher gay stigma scores were less likely to be retained in HIV care (OR 0.9, 95% CI 0.8 to 0.9). Among African-American men who had disclosed their HIV status to network members, general stress was associated with good retention (OR 1.2, 95% CI 1.1 to 1.3). Among Latina women who disclosed their HIV status, disclosing their status to more people quintupled chances of retention in care (OR 5.0, 95% CI 1.2 to 20.5). And among African-American women who disclosed their HIV status, those with a higher CD4 count in the last 6 months were 10 times more likely to stay in care (OR 10.4, 95% CI 2.1 to 51.2).



Testing, linking, retaining: An HIV clinician's perspective

An interview with **Michael J. Mugavero, MD**

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Project Director
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Dr. Mugavero is one of a handful of HIV clinicians who closely studies discontinuities in HIV care from diagnosis through referral and retention, both in the 1917 Clinic Cohort at the University of Alabama at Birmingham and through analysis of other research. His recent publications include work on temporal trends in presentation for outpatient HIV medical care in the past decade, health care system and policy factors influencing engagement in HIV medical care, and underutilization of the AIDS Drug Assistance Program (ADAP).

Mascolini: To give readers perspective on your insights based on experience at your own clinic, can you outline the demographics of your patient population?

Mugavero: The University of Alabama (UAB) 1917 Clinic Cohort includes patients who are in care at the UAB 1917 Clinic. We currently have over 1800 patients receiving primary HIV medical care, in addition to other supportive and specialty care. Our clinic population is roughly 50% white and 50% African American, although 80% of our women are African American and 20% are white. In terms of transmission risk,

slightly more than 40% of our patients are men who have sex with men, with the majority of the rest reporting heterosexual transmission. Injection drug use explains HIV transmission in less than 10% of our clinic population. Roughly 35% of new patients in our clinic have private health insurance. The remaining patients have either public health insurance or are uninsured, and insurance status is roughly split between those other two categories.

An influx of new, healthier HIV patients

Mascolini: The CDC estimates that 20% of HIV-positive people in the United States remain unaware of their infection.¹ What's your perspective on the scope of this problem from experience at your clinic and from your understanding of data across the US?

Mugavero: The CDC has wonderful surveillance and epidemiology teams that use sophisticated approaches to track and estimate the number of individuals who are HIV positive and unaware. In our clinic, since 2006 we've observed a dramatic increase in the number of new

HIV patients coming in. It's hard to say whether we can attribute that increase to implementation of the CDC's revised HIV testing recommendations² or to other factors. For example, the Alabama Department of Public Health put into place a new program to enhance referral for treatment services, and we developed a new patient orientation program in our clinic.

It's also hard to say whether the recent increase in new HIV patients in our clinic corresponds to the CDC revising its estimate of infected-but-unaware people from 25% to 20%.¹ Regardless of the cause, this influx of new patients is encouraging. At the same time, we've found that our new patients are coming into care earlier in the course of infection in terms of CD4 count and presence of opportunistic infections. Through 2006, roughly half of our patients presenting for HIV care and never seen elsewhere had a presenting CD4 counts below 200, and about one third had an opportunistic infection before or at presentation to care. From 2006 through the end of 2010, we saw a steady and continuous decline in presentations with low CD4 counts or opportunistic diseases. In the most recent years, 31% of new patients are coming in with a CD4 count below 200, and well below 20% are coming in with an opportunistic infection.

Again, it's hard to say what factors are associated with these changes, but the trend over time is encouraging, and the bolus of new patients coming in earlier supports the idea that we're doing a better job identifying infected people and getting them into care more expeditiously.

Mascolini: Are clinicians you know at other HIV centers across the country telling you they're having the same experience?

Mugavero: I've heard mixed anecdotal feedback from different sites. But an NA-ACCORD cohort analysis of US and Canadian patients from 1997 to 2007 also showed a steady increase in median CD4 count among new patients entering care and a decrease in the proportion of patients presenting with a CD4 count below 350,³ which until recently was the prevailing recommendation of when to start therapy. These changes were less dramatic than our single-site findings, but NA-ACCORD appears to be the largest national study that suggests persons newly entering care are doing so at an earlier disease stage.

Mascolini: Your study of late diagnosis at Duke University in North Carolina found associations between late diagnosis and both older age and female gender.⁴ What explains those associations and what other factors contribute to late diagnosis in the United States?

Mugavero: First it's important to note that this was a fairly small, single-site study.⁴ We assessed about 100 patients in that study. The findings for older age and late diagnosis have been seen fairly consistently across different settings in recent years.⁵⁻⁸

Several factors may contribute to that association. First, perceived likelihood of becoming infected with HIV probably declines with age among individuals as well as their health care providers. There may well be a misconception that older individuals are less likely to be at risk. The other factor that may contribute is length of time since infection: Some people diagnosed with HIV infection at an older age probably became infected years earlier, so they had had more time to experience CD4 decline

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and more advanced infection at the time of testing positive.

The gender finding in our study is interesting.⁴ We found that women were more likely than men to be diagnosed with HIV during hospitalization (adjusted odds ratio 6.74, 95% confidence interval 2.08 to 21.81, $P = 0.001$). We didn't have enough details to know whether some of those hospitalizations might be related to pregnancy or what specifically caused those hospitalizations. We did *not* see that women had lower CD4 counts than men at presentation. Actually, a number of studies found that women are often diagnosed at a higher CD4 count than men.^{5,6,9} I think part of that success can be explained by the long-standing recommendation for routine HIV screening during pregnancy, which was in place long before the CDC's 2006 recommendation for general opt-out screening.²

Addressing system-level hurdles to linkage and retention

Mascolini: Turning to linkage to care, a fair amount of research has focused on patient-related factors affecting late entry to care. You published an interesting analysis of health care system and policy factors that influence linkage to care.¹⁰ How do you weigh the relative importance of these two sets of factors?

Mugavero: Both sets of factors are critically important, so you can't necessarily weigh the importance of one against the other. In that paper we explored a socioecological model that looked beyond individual sociodemographic characteristics to relationship characteristics and factors related to the community, the healthcare sys-

tem, and healthcare policy.¹⁰ Most HIV linkage studies have looked at individual-level factors—often at very fixed sociodemographic variables such as age, race, sex, and insurance status—as they relate to delayed entry to care. But it's also important to assess how system-level and policy-level variables influence linkage and retention because system-level changes, if successful, can have broad reach. Addressing system-level obstacles can complement individual-level interventions and expand their scope.

For example, re-emergence of ADAP waiting lists in recent years illustrates how a policy factor can influence testing uptake and linkage to care. When people at risk for HIV or recently diagnosed with HIV see news stories about perceived or real lack of availability of medications, those stories can be a disincentive to getting tested or getting into medical care. The impact of news about something like an ADAP waiting list on testing and care decisions is hard to measure, but I think variables like these can have a great impact.

As another example of system-level factors, a number of studies show that when testing and medical services are located at the same site, people are more likely to get linked into care and are more likely to get linked expeditiously.^{11,12} So, at a system level, having those services co-located can help.

Another system-level variable is the waiting time between calling to make a first appointment in an HIV clinic and the actual date of that appointment.¹³ HIV is a life-changing diagnosis for everyone. In the weeks after that diagnosis, individuals go through a range of emotions and psychological stresses. Linking that person to care gives them access to so many resources be-

sides medical treatment—resources that really help them take the next steps in entering care, educating themselves, and assuming responsibility for self-care and disease management. The sooner you can make that bridge from the community to the clinic, the better.

Mascolini: Your study of the “no-show phenomenon” implicated gender, race, lack of insurance, and a long waiting time to the first appointment date as determinants of poor linkage to care.¹³ Clinicians can’t do anything about their patients’ gender, race, or insurance status. What have you done to address the waiting-time factor?

Mugavero: Historically, at our clinic the waiting time was up to 4 weeks from someone calling to schedule a first appointment until a health care provider was available. That waiting time actually increased recently to between 4 and 6 weeks. When you think about how much happens in a person’s life in 4 to 6 weeks, especially at such a vulnerable time after testing positive

for HIV, it’s easy to see how readily barriers might arise to taking the next step and getting into care.

After we did that waiting-time analysis,¹³ we brought together a multidisciplinary team of stakeholders in the clinic and developed a new patient orientation program. First, we agreed that 4 weeks is too long for a first-time patient to wait and probably partly explains why one third of potential patients were not getting into care. Because the clinic didn’t have the capacity to shorten the time to the provider visit, we developed a new patient orientation visit. We call it Project CONNECT.¹⁴

Other sites have different types of orientation visits—a lab-only visit or a brief nursing visit. Project CONNECT is a detailed patient-focused visit led by social work services and including a semistructured interview, a psychosocial questionnaire, and baseline laboratory testing (**Figure 1**). The interview aims to assess how new patients are adjusting to their diagnosis,

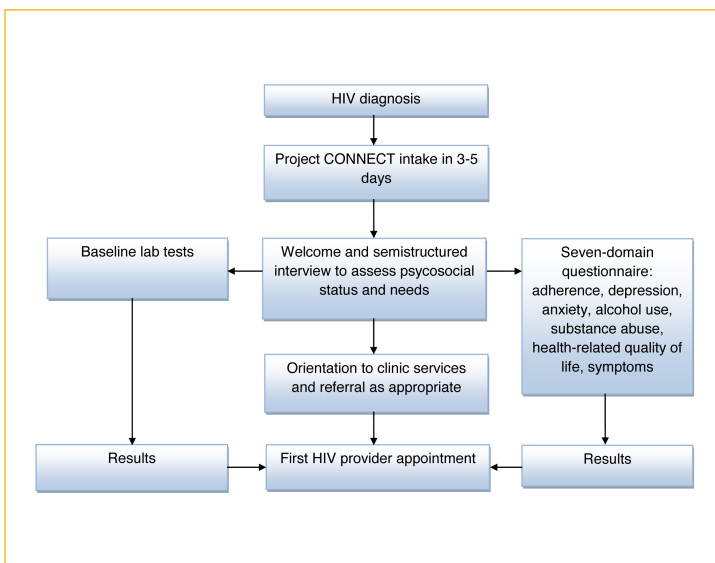


Figure 1. Project CONNECT at the University of Alabama 1917 Clinic aims to bring people to the clinic within 3 to 5 days of HIV diagnosis, to orient them to HIV care and address immediate concerns, and to begin collecting data the medical provider can use at the first care visit.

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while the questionnaire captures information about depression, anxiety, substance use, alcohol use, and other factors that may be impediments to staying in care, starting therapy, and staying on medications. The orientation visit also lets individuals know what resources are available to them at the clinic.

All of this information—expansive contextual and behavioral information in addition to baseline lab work—lets the medical provider engage the patient immediately at the first provider visit. As a result, the clinician begins care for a new patient with rich information about social support, stigma, disclosure, depression—many potentially modifiable factors that may present challenges to staying in care.

The CONNECT visit occurs within 3 to 5 days of someone calling, sometimes even sooner. The idea is that the sooner we can get someone from the community to the clinic, the sooner we can make that personal connection, have someone welcome them, and have someone address their early questions and concerns. If we can make that strong connection up front, it will help get new patients to the medical provider visit, make the first provider visit more meaningful and productive, and provide a foundation for successful partnerships in managing HIV.

Talking to patients about retention

Mascolini: You and others have outlined an array of factors that can be addressed to improve linkage to care.¹⁴ Besides shortening the time to a new patient's first clinic visit, what other factors can clinicians address to get more newly diagnosed people into care?

Mugavero: Testing is often done in nonmedical settings or at least not in an HIV medical clinic. Many people are diagnosed after testing in outreach settings, emergency departments, or hospitals and are then reported to the health department and referred to an HIV clinic. One thing clinicians can do is to develop relationships—memoranda of understanding—for how to work with these community partners on linkage to care. The key factor is determining how to integrate service delivery and work together.

Once someone makes it to clinic, the provider should talk openly about retention in care within the paradigm of adherence. When I give talks about these issues and ask providers how often in their encounters they talk about medication adherence, it's over 90%. Medication adherence has become engrained in our culture of providing care as HIV clinicians. I similarly encourage clinicians to talk to patients about retention in care—not just adherence to meds, but adherence to visits.

Even brief statements can be validating: "It's great to see you today. I'm glad you made it in." If someone misses a visit, the provider should acknowledge that: "I missed seeing you last time. What's going on? What was happening?" Just paying attention to the fact that you as a provider notice whether or not a patient comes to visits and that you care sends a strong message. It's a relatively simple thing to do, and anecdotally patients respond to it.

I was encouraged to see that one of the new recommendations in the 2009 HIVMA guidelines is expanding the notion of HIV adherence beyond medication adherence to include retention in care.¹⁵ That was really encouraging because, when you look at the grand scheme of things, among all persons with HIV in the US, only a

small proportion is on antiretroviral therapy.¹⁶ A lot of infected people are not linked or not retained, so we've got to pay more attention to those aspects if we're going to have maximal reach.

Mascolini: A study at your clinic determined that missing visits in the first year of HIV care more than doubled the rate of long-term mortality.¹⁷ Other studies yielded similar findings.¹⁸⁻²⁰ What are the variables that raise the risk of poor retention in your clinic, and what have you done to address those factors?

Mugavero: When you look at a lot of the literature, we're focusing on factors like age and gender and race, which might help identify risk groups, but these are not modifiable factors. As the field moves forward, it's critical that we start looking at modifiable factors that might influence linkage and retention in care.

Factors that we and others have noticed include common co-occurring disorders: Depression, anxiety, substance use, and alcohol use are associated with worse retention in our clinic. By asking new patients about some of these factors during our initial CONNECT interview, we can identify individuals up front who are at high risk for worse retention in care and worse medication adherence once therapy begins. By identifying those factors early, we can refer people to appropriate services and make primary providers aware of these factors at the first clinical visit. I think screening, identifying some of those factors, and referring to appropriate treatment can be critical.

This screening and assessment should not happen once, but on an ongoing basis. These are things that can be done systematically within a clinic.

Working toward a seamless continuum of care

Mascolini: When I was doing research for these articles on testing, linkage, and retention, I saw that many studies are done by people on the policy side or in epidemiology or other non-clinical fields. You're one of a handful of HIV clinicians who have studied these issues closely. What was your motivation for getting into this area of research?

Mugavero: From 2003 to 2006, when I was an infectious diseases fellow working on expanding HIV testing, I began to realize the challenges beyond HIV testing and started thinking about the obstacles to ensuring a continuum of care. Much of my research focused on testing, and then in the clinic I was caring for a lot of people with HIV, but I realized that many barriers and challenges lay between those two points. It became clear that the folks I was seeing in clinic were just a subset of those I was trying to reach with the testing efforts.

To me this continuum seemed a natural progression of the focus on medication adherence. If large numbers of individuals are unaware of their infection, or not linked to care or retained in care, the impact of successful treatment and adherence interventions on a population is greatly diminished.

In the last 3 to 5 years we've seen a dramatic expansion in emphasis on linkage and retention in care. A lot of that is driven by the test-and-treat paradigm or TLC-Plus: test, link to care, plus treatment.²¹ This approach—expanded HIV testing plus quick linkage to care and treatment—should have benefits both for the individual and at the population level because

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identifying infected people and treating them quickly will lower “community viral load” and limit HIV transmission. We saw this in HPTN 052, an international randomized trial that ended early when antiretroviral therapy begun at a higher CD4 count for the positive partner in a discordant couple lowered the risk that the negative partner would become infected by 96%.²² Those results should stimulate even more interest in the test-and-treat concept.

I always stress that we need integrated approaches not just from a research perspective, but also from a practical perspective across this continuum of care (**Figure 2**). A newly diagnosed person doesn’t think, “Now I’m going to go to my outreach intervention. Now I have to hop over to linkage to care. Now that I’ve made it to clinic, I’m going to focus on risk reduction, then on starting therapy, then on adherence.”

Our approaches to these interventions often focus on one piece at a time, and we do need to focus on each element. But ultimately, if we really want to have impact, we need integrated approaches that map to the lived experience. Someone should go seamlessly from testing positive to getting into care, developing early behaviors around starting therapy, having good adherence to visits and to medicines—all in a matter of months. Although test-and-treat and TLC-Plus focus on secondary prevention and population health, I think they have incredible potential to improve individual health outcomes.

Mascolini: Before we close, would you like to make any other points related to any of these issues?

Mugavero: I think the key message is that improved HIV care is going to require integra-

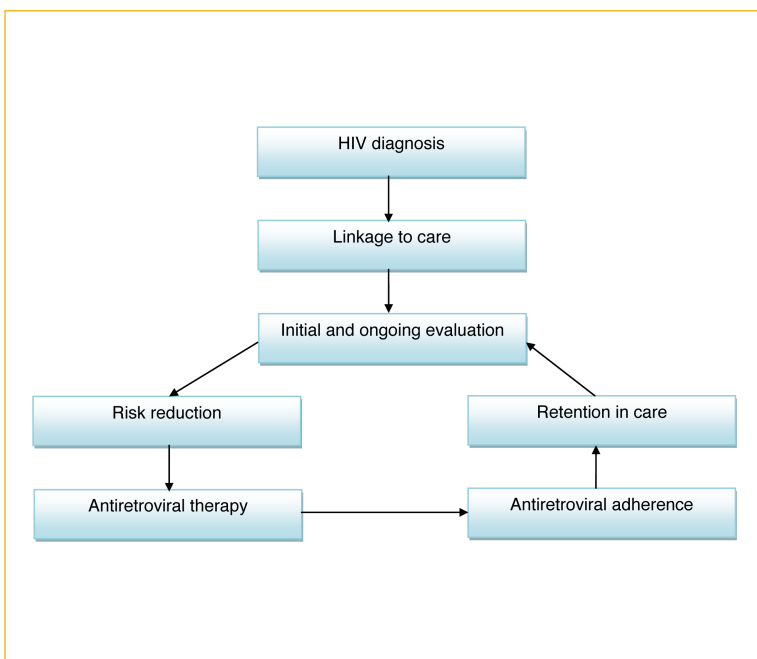


Figure 2. This simplified scheme of HIV care from diagnosis through antiretroviral therapy and retention in care indicates that care should be viewed as a seamless continuum, not a series of discrete steps.

tion at multiple levels—both scientifically and in practice. And over the past few years we have seen more and more integration, at the funding level and in local service delivery between medical providers, AIDS service organizations, community-based organizations, and health departments. The overriding idea is that we need approaches from testing through outcomes that match the individual's experience. People with HIV don't seek services piecemeal in discrete steps; there should be a seamless transition from one facet of care to the next.

With TLC-Plus²¹ and other studies, we need to determine the best way to integrate efforts and meet individuals' needs. Right now we're losing too many HIV-positive people at each step along that cascade who are not diagnosed, not linked, not retained. We must redouble our efforts to focus on helping people navigate this continuum of care as seamlessly as possible.

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