Rapid HIV self-testing: long in coming but opportunities beckon

Julie E. Myers[a,b], Wafaa M. El-sadr[c], Allison Zerbe[c] and Bernard M. Branson[d]

The recent approval by the United States (U.S.) Food and Drug Administration of a rapid HIV self-test marks a significant milestone in the evolution of HIV testing approaches. With nearly one in five people living with HIV in the United States still undiagnosed and an even higher proportion unaware of their infection globally, this decision reflects a new willingness to offer diverse options to get tested for HIV. Rapid self-testing offers several distinct opportunities to improve testing among those with undiagnosed HIV: to encourage testing among those who might not otherwise be tested, to increase the frequency of testing among persons at highest risk for new infection, and to facilitate mutual HIV testing with sex partners. To date, the path to regulatory approval has been long but instructive. The studies and clinical trials required for regulatory approval in the U.S. provide insight into the performance and potential implications of HIV self-tests as they become available for sale directly to consumers. Although some persistent reservations about self-testing for HIV remain, including the ''window period'' of the current test kit, its cost, and its effectiveness for facilitating entry to medical care, others have been dispelled. Self-testing in resource-constrained settings is also promising, including self-testing of health professionals. At present, although the impact has yet to be determined, availability of this new option may offer potential opportunities to improve HIV diagnosis and facilitate both treatment and prevention.

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Introduction

Nearly one in five people living with HIV in the United States (U.S.) are unaware they are infected [1]. Globally, approximately 60% of those with HIV are unaware [2]. Persons who are unaware of their infection account for almost half of all sexual transmissions in the U.S. [3] and contribute disproportionately to the continued spread of HIV. Thus, HIV testing remains essential to HIV prevention efforts in the U.S. [4,5] and worldwide [6]. Prompt identification of HIV infection offers many benefits to both the individual and community. In the U.S., antiretroviral therapy (ART), with the goal of viral suppression, is now recommended for all persons with

[a]New York City Department of Health and Mental Hygiene, New York, USA, [b]Division of Infectious Diseases, Department of Medicine, Columbia University Medical Center, New York, USA, [c]ICAP, Mailman School of Public Health, Columbia University, New York, USA, and [d]Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

Correspondence to Julie E. Myers, MD, MPH, Bureau of HIV/AIDS Prevention and Control, New York City Department of Health and Mental Hygiene, 42-09 28th Street, 22nd floor, Queens, NY 11101.

Tel: +347 396 7761; fax: +347 396 7791; e-mail: jmyers@health.nyc.gov

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Table 1. Five FDA-approved, CLIA-waived rapid HIV antibody screening tests.

Test type	FDA Approval Received	Specimen Type[a]	Manufacturer	Approved for HIV-2 Detection?
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	Nov 2002	Oral fluid Whole Blood (fingerstick or venipuncture)	OraSure Technologies, Inc.: www.orasure.com/products-infectious/products-infectious-ora-quick.asp (Bethlehem, Pennsylvania)	Yes
Uni-Gold Recombigen HIV	Dec 2003	Whole blood (fingerstick or venipuncture)	Trinity Biotech; www.unigoldhiv.com; (Jamestown, New York)	No
Clearview HIV 1/2 STAT-PAK	May 2006	Whole Blood (fingerstick or venipuncture)	Alere, Inc. (formerly known as Inverness Medical Professional Diagnostics); www.alere.com/EN_US/index.jsp; (Waltham, Massachusetts)	Yes
Clearview COMPLETE HIV 1/2				
INSTI HIV-1 Antibody Test	Nov 2010	Whole Blood (fingerstick)	bioLytical Laboratories, Inc.; www.biolyticalus.-com (Richmond, British Columbia, Canada)	No

[a]Specimens types for which the tests are CLIA-waived. The tests are categorized as moderate complexity under CLIA if used with serum or plasma.

HIV infection [7]; in resource-constrained settings, WHO has recommended antiretroviral therapy for all persons with a CD4 cell count of <350 cells/μL and for the HIV-positive partner in serodiscordant couples [8,9]. Durable viral suppression improves immune function and quality of life, decreases morbidity and improves survival [7]. HIV-positive persons in the U.S. appear to reduce high-risk sexual behavior after they become aware of their diagnosis, at least temporarily [10]. Mathematical models provide support that early ART initiation would decrease HIV transmission [11–15] and findings from the HIV Prevention Trials Network 052 study [16], which documented this benefit, further stimulated interest in scaling-up HIV testing and using of ART for prevention. Thus, additional effective methods are needed to increase HIV testing Table 1.

Self-testing, with its convenience, privacy and anonymity, might present a promising option. With approximately 208,000 persons with undiagnosed HIV infection in the U.S. alone, 50,000 annual new infections in the U.S. [17] and 2.7 million globally [2], it is essential to promptly identify HIV-infected persons.

Rapid self-tests: possible roles

Rapid self-testing offers several potential opportunities. Firstly, it might be used by persons in high-prevalence communities who have eluded previous prevention and testing efforts [18]. In the U.S., the proportion of persons with undiagnosed infection is highest among racial and ethnic minorities and young people; an estimated 68% of all persons with undiagnosed HIV are black or Hispanic [1] and 60% of persons aged 13–24 years with HIV are unaware of their infection [1]. These same populations, i.e., racial and ethnic minorities and young people, expressed high levels of interest in using rapid HIV self-tests in a 2006 population-based telephone survey in New York City (NYC) [19]. Men who have sex with men (MSM), a population at high risk in the U.S.[5], were the subject of an online survey in six cities; among those who had never been tested for HIV, 86% of those likely to get a test in the next year expressed strong intentions to use a rapid self-test, if available [20]. A majority (87%) of MSM surveyed online in France were interested in self-tests, if available; interested men were more likely to have never tested or to have not tested in the past year, and to live their sex lives with men "in absolute secrecy" [21]. The small proportion of the MSM (3.5%) in the study who had already accessed unapproved tests online had similar characteristics [22].

A second prospect for rapid HIV self-tests might be to facilitate more frequent testing among persons at highest risk for HIV. CDC guidelines recommend HIV testing at least annually for individuals at high risk of HIV [23,24]. More frequent testing is necessary for populations with high incidence, and the convenience of self-testing could facilitate this. In the 2008 U.S. National HIV Behavioral Surveillance (NHBS), HIV prevalence was 19% among MSM; nearly half (44%) were unaware of their infection [25]. Although 61% of the MSM recruited from venues in 21 metropolitan areas reported testing for HIV within the preceding 12 months, 7% of these had a new, positive HIV test [25]. Fully 45% of the MSM who were unaware of their infection had been tested within the preceding 12 months [25]. Similarly, among MSM in a study of HIV self-testing at a Seattle sexually transmitted infections (STI) clinic, 84% said they would test more frequently with a rapid self-test – depending on its cost [26].

A third potential for rapid self-test is that such tests might facilitate mutual HIV testing with sex partners or even "point-of-sex" testing [27]. During in-depth interviews with HIV-negative MSM in NYC who never or rarely used condoms, 80% indicated that they would likely use an over-the- counter rapid HIV test to test sex partners (some with new partners and others indicated with established partners) [28]. In a follow-up study, 27 participants who received rapid test kits used them before planned intercourse with approximately 100 prospective

sex partners; some of the kits were also used to test acquaintances [29]. No sexual intercourse took place after a detected positive test, and most participants said that having and using rapid HIV test kits shifted their perceptions of risk and led to changes in behavior [29].

Availability of rapid HIV self-tests offers a fourth opportunity. Such tests could be used to help detect "window period" infections by repeat testing several weeks after a negative HIV test in persons with very recent potential exposure to HIV. Rapid tests in wide use in the U.S. and globally detect only IgG antibodies and have an estimated window period of 25–35 days [30,31]. Studies at HIV testing programs in STI clinics demonstrated that, among patients with undiagnosed HIV, 5% of those in Malawi [32], 9% of those in NYC and 20% of MSM in Seattle had detectable HIV RNA despite a negative rapid antibody test [33,34].

Self-testing for HIV: old concept, new opportunities

The concept of self-testing for HIV is not new. Home collection kits for HIV testing were first proposed in 1986. However, professional organizations, public health agencies, and gay activists expressed concern that the tests might be inaccurate or increase the risk of suicide [35]. In addition, the U.S. Food and Drug Administration (FDA) expressed concern about the safety and efficacy of obtaining HIV test results without professional supervision. Nonetheless, in 1996, the FDA approved two home sample collection kits for HIV as technology advanced and desire for greater personal autonomy for health care decisions grew [35]. Both involved self-collection of dried blood spot specimens that are mailed to a laboratory for testing with access to test results by telephone [35]. Post-marketing data demonstrated that the kits were used by persons at risk and by those with no other access to HIV testing; more than half (including half with positive tests) had not been tested previously [36]. However, home sample collection kits were not widely adopted by persons at high risk for HIV infection [37].

Prospects for true self-testing for HIV changed considerably with FDA's approval, in 2002, of rapid HIV tests eligible for waiver under the Clinical Laboratory Improvement Amendments (CLIA) [38], and their subsequent widespread use (even though their sale was limited to agents of a clinical laboratory) [39]. Rapid HIV tests significantly increase the number of people who learn their test results [40] and are preferred by high-risk persons [41] and those not previously tested [42].

Experiences with HIV self-testing

Three U.S.-based studies conducted with the oral fluid HIV test use demonstrated self-testing was feasible and persons were willing to perform the test. In an emergency department study in a Baltimore hospital, rapid HIV self-test results were 99.6% concordant with results of tests performed by health care professionals; 97% of participants agreed that oral fluid samples were "not at all hard to collect" [43]. In a randomized study of unobserved self-test use among MSM in Seattle, 68 men received a kit, 45 of whom obtained 100 additional kits for subsequent testing. Among 43 men who completed 69 surveys about the kits, it was noted to be "very easy to use" on 66 (96%) surveys and "somewhat easy to use" in the other three [26]. Among 42 MSM in a self-testing study in NYC, most participants performed the test without mistake while being observed [28]. International studies found similar results. In Malawi, 260 (92%) of 283 study participants elected an oral fluid self-test after a demonstration. Accuracy was 99.2% (2 of 48 participants with positive finger-stick blood rapid tests obtained negative oral fluid self-test results). Although 98.5% of participants agreed that the test was "not at all hard to do," 10% made minor procedural errors, and 10% required extra help [44]. A study of oral fluid self-testing in Singapore had similar findings [45]: 977 (99.1%) obtained correct results, and more than 80% said they would purchase a self-test.

The path to regulatory approval

In some countries, rapid HIV tests have been available over-the-counter for several years (e.g., in Hong Kong and Macao since 2005 [46] and in South Africa since 2007 [47]). In other countries, including the United Kingdom and Australia, sale of HIV tests to the public is prohibited [48,49], although HIV self-tests of uncertain accuracy are available directly via the internet [50].

In 2005, after review and public testimony, an FDA advisory committee concluded that self-testing offered potential for public health benefit and later established criteria to allow FDA approval [51]. These included a minimum threshold for accuracy, acceptable performance in a "real-world" context, and validation of instructional materials demonstrating that users understood the accuracy and limitations of the test (including the "window period"), and correct interpretation [52].

In 2012, the manufacturer of the oral fluid HIV self-test, OraSure Technologies (Bethlehem, Pennsylvania) submitted data to the FDA on 5,800 subjects recruited for unobserved self-testing [53] and presented these to the FDA advisory committee [54]. Label comprehension exceeded 80% on all aspects of performing the test and

interpreting the results [55]. Of 5662 individuals who received test kits (Fig. 1), 4562 (82%) were from high-prevalence populations (10% MSM and 90% high-risk heterosexuals). Only 56 (1.11%) users were unable to obtain a result ("test system failures"); 88 self-test results were true-positive, 8 false-negative, 4902 true-negative, and 1 false-positive. HIV prevalence was 2.12%, sensitivity of the self-test 91.67% (95%CI: 84.24–96.33%) and specificity 99.98% (95%CI: 99.89–100.0%) [55].

Although the test's sensitivity did not meet the recommended minimum requirement, FDA constructed a Monte Carlo model to evaluate the test's potential public health risks and benefits. The model predicted, based on the results of the clinical trial, that 2.8 million

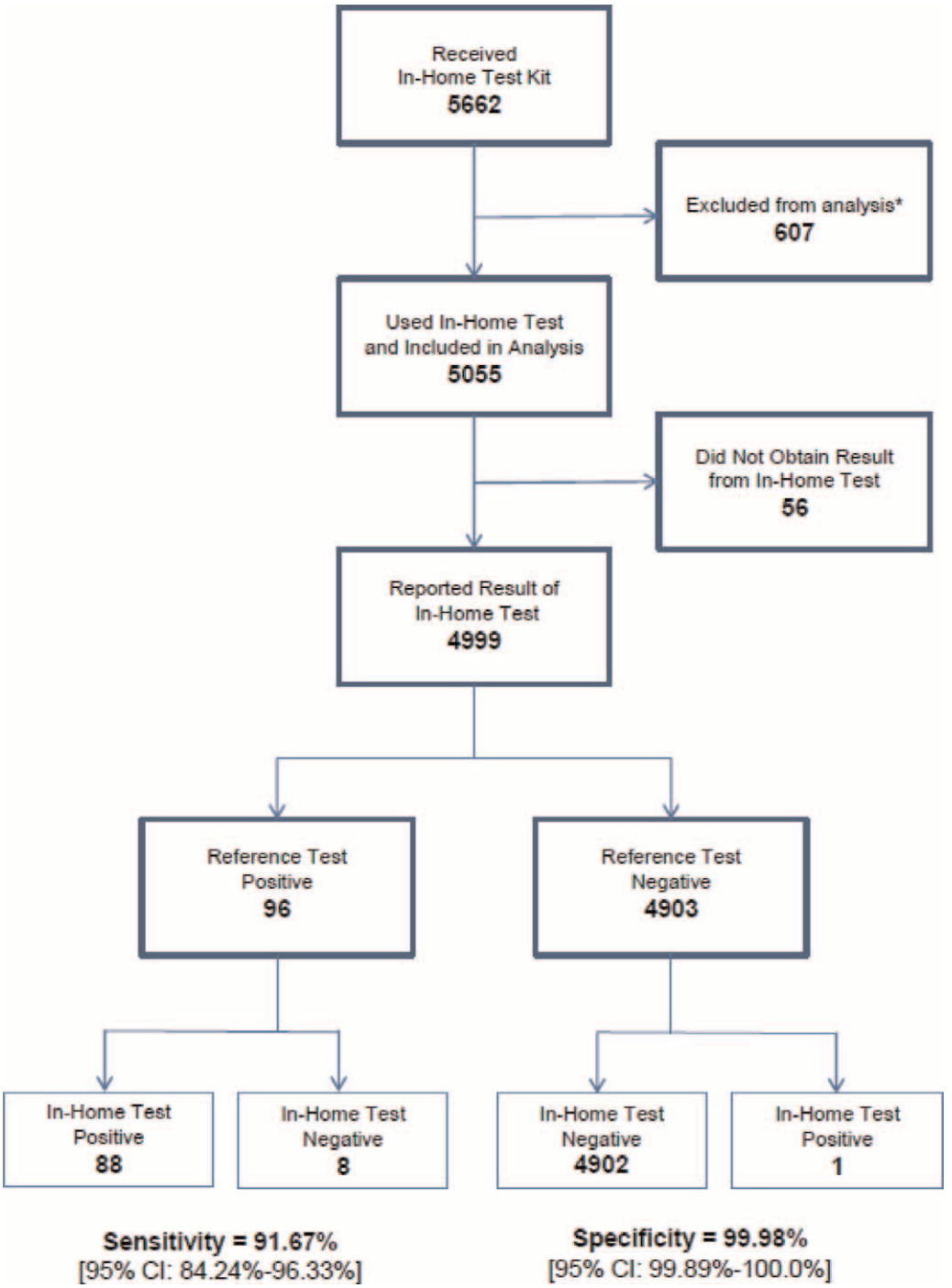

Fig. 1. Disposition of subjects in analyses populations of OraSure Technologies phase III clinical trial data submitted to the FDA [56].

persons with a seropositiviy of 1.6% would use the self-test during the first year, yielding 45,000 true-positive and 3,800 false-negative test results [56]. Based on the assumption that 8–10 transmissions would be averted for every 100 persons who learned they were HIV-positive [3], the model predicted that the self-test might avert more than 4,000 new transmissions of HIV. False-negatives due to the test's sensitivity had implications for individual health, but sensitivity had little impact on the number of net transmissions averted in the model: 4,100 at 84% sensitivity; 4,600 at 96%. Based on this information, the FDA approved the oral self-test (OraQuick In-Home HIV Test) on July 3, 2012. However, the predicted HIV seropostivity rate of 1.6% might be an overestimate. In the clinical trial, the low prevalence population had a seropositivity of only 0.09%; a population with such a prevalence might be expected to be more representative of kit users [57].

Concerns about self-testing: some dispelled, some remain

Several reservations have been expressed regarding self-testing including: 1) concerns about correct interpretation, emotional consequences of a positive result, and theoretical misuse; 2) the test's suboptimal sensitivity and window period of up to three months; 3) cost; 4) its effectiveness for facilitating entry to care; and 5) the possibility of "risk compensation" (that frequent testing or testing before sexual encounters might lead to increased risk behavior).

Lack of counseling and supervision is inherent to self-testing, and mental distress or even suicide after a positive test result is possible [58,59]. However, home sample collection for HIV has proceeded for more than a decade without documentation of adverse consequences [36,59], and concerns about suicide have not been substantiated [35,60]. Evidence suggestive of increases in suicide comes from older studies prior to availability of effective ART [61,62]. A large study of military recruits did not find a statistically significant increase in the risk of suicide in the months immediately following a positive HIV test [63]. The availability of effective ART has also changed perception of the disease. In fact, some at-risk individuals have reported *reduced* anxiety [64] or feeling "calm" [55] upon learning their results.

Concern also persists about the self-test's sensitivity compared with professional-use tests on blood specimens and the possibility that unsupervised self-testing might lead to false reassurance during the acute HIV infection "window period" [65–67]. These concerns might be especially relevant for the same high-risk populations who expressed specific interest in self-testing. In the study of MSM at the Seattle STI clinic, 16 (8%) of 192 HIV-infected patients had a negative OraQuick rapid test but positive enzyme immunoassay, and an additional 23 (12%) had detectable HIV RNA but no detectable antibody [34]. However, this limitation is applicable to all rapid HIV tests whether conducted by professionals or via self-test, and highlights the importance of frequent retesting in high risk individuals. Despite the window period, screening prospective sex partners before sex with a rapid HIV test might help reduce HIV transmission [29,68]. One model of transmission among MSM who never used condoms determined that rapid HIV self-testing with unprotected intercourse after a negative result led to a lower probability of HIV infection. However, this benefit was lost if condoms were used in at least one in four sexual encounters [68].

The price for the self-test kit might affect its potential public health benefits [18,69] if its adoption is limited only to those who can afford it, rather than those who need it [69]. The current retail price of the FDA-approved test in the U.S. is $39.99. In the report of the 1998–99 HIV Testing Survey, among the 939 participants who had heard of home collection kits but had not used them, kit cost was the third most common concern (34%) after concerns about accuracy (56%) and lack of in-person counseling (47%) [37]. Among heterosexuals in urban areas of the United States, HIV prevalence rates are inversely related to socioeconomic status [70], and HIV diagnosis rates among all adults and adolescents are higher in communities with a lower socioeconomic composition [71]. Thus, the populations in greatest need of an HIV test might be the least able to pay for it [69]. In NYC, among persons who considered self-testing acceptable, approximately half reported some financial barriers to its purchase [19]. MSM in the Seattle study were also sensitive to price: only 17% would pay $40 or more for a kit [26]. In Spain, 17.9% would pay $38 or more [72], but in Singapore, only private clinic attendees were willing to pay up to $15 [45].

A major concern about the HIV self-test is whether some persons might fail to seek confirmatory testing or medical care after a positive test result. With the home collection kit, 65% of HIV-positive users accepted referrals for medical care, and 23% already had a source of care [36]. In the clinical trial of the self-test, 88% of those testing positive reported they would "definitely" follow-up with a doctor or clinic; another 8% were "highly likely" to do so [55]. These results are reassuring, but in the clinical trial, follow-up contact was required, and, thus, responses were not necessarily representative of eventual users. In the Seattle self-test study, one sex partner of a study participant tested positive with a kit obtained from the participant, assumed that the test result was definitive, and did not seek timely confirmatory testing or follow-up care [73].

Finally, it is not known whether persons who use self-tests might adopt riskier behaviors (i.e., risk compensation) after receiving "good news" (a negative self-test result). Although risk compensation has not been noted in recent large trials with frequent HIV testing in conjunction with pre-exposure prophylaxis [31] and male circumcision studies [74], these trials also included intensive risk-reduction counselling. In contrast, one observational study suggested that increased risk behavior might occur after non-occupational post-exposure prophylaxis [75]. Further, in a vaccine preparedness study that included quarterly HIV testing and counseling, more than half of MSM whosubsequently seroconverted reported unprotected anal intercourse after study visits at which they tested negative. This decreased substantially after they received their HIV-positive test result [76]. Definitive answers might await an ongoing clinical trial randomizing MSM to a rapid self-test or a clinic-based test to determine the effects of self-tests on the frequency of testing and risk behaviors [77].

Strategies for Use of HIV self-tests

The optimal self-testing paradigm has yet to be established, but a number of alternatives might be feasible. Distributing HIV self-tests through internet solicitations might help reach and increase testing frequency among persons at high risk of HIV acquisition, such as MSM who seek both sexual partners and health information online. Persons visiting social networking sites and urban sexual health clinics are willing to receive HIV testing materials through the mail [78,79], and French MSM participating in an online survey confirmed their willingness to obtain HIV self-tests online [21]. Alternatively, persons with ongoing HIV risks who seek testing could be invited to distribute kits to their social and sexual networks. Use of social networks to recruit persons for testing has proven successful for identifying a high percentage of persons with undiagnosed HIV [80].

Self-testing in resource-constrained settings

Although much of the research and discussion about self-testing has been focused in the U.S. and Europe, such tests also hold promise for resource-constrained countries. Nearly all of 257 heterosexual participants in the community-based study of self-testing in Malawi expressed willingness to test themselves in the future, and all would recommend self-testing to friends and family [44]. However, special challenges in this context include the inability to offer counseling when access to telephones or internet is limited, and the difficulty in obtaining HIV care and treatment for those who test positive. Obstacles to procuring test kits, either due to cost or supply chain logistics, might be another barrier [81]. The lack of regulation to ensure quality of self-testing products poses another challenge [58,59]. However, support for a self-testing paradigm is already mounting [2], especially as a strategy to increase rates of HIV testing among health care workers in Africa [58], and Kenya's National Guidelines for HIV testing and counseling now include self-testing as a possible option [82].

Looking ahead

As the HIV epidemic continues into its fourth decade, rapid HIV self-tests might offer a new tool to increase the number of persons with HIV who become aware of their infection [83], particularly if the tests are affordable or if test kits can be subsidized for persons at high risk to expand testing and to expedite earlier diagnosis, two key elements of strategies for control of HIV globally.

Yet many questions remain unanswered. Who will ultimately purchase and use the test? Will persons at risk substitute the less sensitive self-test for professional testing, with its better sensitivity? Will those at high risk who have been unwilling to test for HIV use self-tests [18,57,69])? Will cost of the test limit its adoption among those who could benefit the most? What will be the rate and public health impact of false-negative results in various populations? Will persons with a positive self-test seek follow-up testing and ultimately access medical care?

Finally, the approval of the first self-test kit by the FDA will likely stimulate development of other, potentially better self-test kits. Rapid tests with shorter window periods (e.g., fourth-generation antigen-antibody combination assays) are already available outside the U.S [84], and may, in the future, represent a viable over-the-counter option, based on a recent user feasibility study [72]. Regardless, it is important that policymakers, public health leaders, clinicians and researchers continue to explore ways to evaluate new tools and bring them into the hands and homes of those most at risk of HIV acquisition. The HIV self-test may be an important step forward on this path.

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References

1. CDC. **Monitoring selected national HIV prevention and care objectives by using surveillance data-United States and 6 U.S. dependent areas–2010.** *HIV Surveillance Supplemental Report* 2012; 17(No. 3, part A). http://www.cdc.gov/hiv/surveillance/resources/reports/2010supp_vol17no3/index.htm. [Accessed 17 August 2012]
2. **Joint United Nations Program on HIV/AIDS (UNAIDS).** *UNAIDS World AIDS Day Report* 2011, 2011. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/jc2216_worldaidsday_report_2011_en.pdf.
3. Hall HI, Holtgrave DR, Maulsby C. **HIV transmission rates from persons living with HIV who are aware and unaware of their infection.** *AIDS* 2012; **26**:893–896.
4. **Vital Signs: HIV Prevention Through Care and Treatment - United States.** *MMWR Morb Mortal Wkly Rep* 2011, **60**:1618–1623.
5. Office of National AIDS Policy. *National HIV/AIDS Strategy*. In. Washington, DC: Office of National AIDS Policy; 2010.
6. WHO. Global health sector strategy on HIV/AIDS 2011–2015, 2011. http://whqlibdoc.who.int/publications/2011/9789241501651_eng.pdf. [Accessed December 27 2012].
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. [Accessed 16 August 2012].
8. WHO. WHO Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2010. http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf. [Accessed December 27 2012].
9. WHO. WHO Guidance on Couples HIV Testing and Counseling Including Antiretroviral Therapy for Treatment and Prevention in Serodiscordant Couples: Recommendations for a Public Health Approach, 2012 April. http://apps.who.int/iris/bitstream/10665/44646/1/9789241501972_eng.pdf. [Accessed December 27 2012].
10. Marks G, Crepaz N, Senterfitt JW, Janssen RS. **Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs.** *J Acquir Immune Defic Syndr* 2005; **39**:446–453.
11. Bendavid E, Brandeau M, Wood R, Owens D. **Comparative Effectiveness of HIV Testing and Treatment in Highly Endemic Regions** [Abstract 999] In: 17th *Conference on Retroviruses and Opportunistic Infections*. San Francisco, California; 2010.
12. Dodd PJ, Garnett GP, Hallett TB. **Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings.** *AIDS* 2010; **24**:729–735.
13. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. **Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.** *Lancet* 2009; **373**:48–57.
14. Wagner BG, Blower S. **Voluntary universal testing and treatment is unlikely to lead to HIV elimination: a modeling analysis.** *Nature Precedings* 2009. http://precedings.nature.com/documents/3917/version/1/files/npre20093917-1.pdf.
15. Charlebois ED, Das M, Porco TC, Havlir DV. **The effect of expanded antiretroviral treatment strategies on the HIV epidemic among men who have sex with men in San Francisco.** *Clin Infect Dis* 2011; **52**:1046–1049.
16. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, *et al*. **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med* 2011; **365**:493–505.
17. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, *et al*. **Estimated HIV Incidence in the United States.** *PLoS One* 2011; **6**:e17502.
18. Walensky RP, Paltiel AD. **Rapid HIV testing at home: does it solve a problem or create one?** *Ann Intern Med* 2006; **145**:459–462.
19. Myers JE, Bodach S, Cutler B, Shepard C. **Acceptability of Home Self-Test Kits for HIV in New York City, 2006** [Abstract 121]. In: *IDWeek*. San Diego, California; 2012.
20. Mackellar DA, Hou SI, Whalen CC, Samuelsen K, Sanchez T, Smith A, *et al*. **Reasons for Not HIV Testing, Testing Intentions, and Potential Use of an Over-the-Counter Rapid HIV Test in an Internet Sample of Men Who Have Sex With Men Who Have Never Tested for HIV.** *Sex Transm Dis* 2011; **38**:419–428.
21. Greacen T, Friboulet D, Blachier A, Fugon L, Hefez S, Lorente N, *et al*. **Internet-using men who have sex with men would be interested in accessing authorised HIV self-tests available for purchase online.** *AIDS Care* 2013; **25**:49–54.
22. Greacen T, Friboulet D, Fugon L, Hefez S, Lorente N, Spire B. **Access to and use of unauthorised online HIV self-tests by internet-using French-speaking men who have sex with men.** *Sex Transm Infect* 2012; **88**:368–374.
23. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, *et al*. **Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings.** *MMWR Recomm Rep* 2006; **55**:1–17; quiz CE11–CE14..
24. Workowski KA, Berman S. **Sexually transmitted diseases treatment guidelines, 2010.** *MMWR Recomm Rep* 2010; **59**:1–110.
25. **HIV testing among men who have sex with men–21 cities, United States, 2008**. *MMWR Morb Mortal Wkly Rep* 2011; **60**:694–699.
26. Katz D, Golden M, Hughes J, Farquhar C, Stekler J. **Acceptability and Ease of Use of Home Self-testing for HIV among MSM** [Abstract 1131]. In: 19th *Conference on Retroviruses and Opportunistic Infections (CROI)*. Seattle, WA; 2012.
27. Branson B. **HIV Diagnosis: New Tests, New Algorithms** [Paper 114]. In: 19th *Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington; 2012.
28. Carballo-Dieguez A, Frasca T, Dolezal C, Balan I. **Will Gay and Bisexually Active Men at High Risk of Infection Use Over-the-Counter Rapid HIV Tests to Screen Sexual Partners?** *J Sex Res* 2012; **49**:379–387.
29. Carballo-Dieguez A, Frasca T, Balan I, Ibitoye M, Dolezal C. **Use of a Rapid HIV Home Test Prevents HIV Exposure in a High Risk Sample of Men Who Have Sex With Men.** *AIDS Behav* 2012; **16**:1753–1760; http://dx.doi.org/10.1080/00224499.2011.647117. [Accessed 16 August 2012].
30. Branson BM, Stekler JD. **Detection of acute HIV infection: we can't close the window.** *J Infect Dis* 2012; **205**:521–524.
31. Masciotra S, McDougal JS, Feldman J, Sprinkle P, Wesolowski L, Owen SM. **Evaluation of an alternative HIV diagnostic algorithm using specimens from seroconversion panels and persons with established HIV infections.** *J Clin Virol* 2011; **52 (Suppl 1)**:S17–S22.
32. Pilcher CD, Price MA, Hoffman IF, Galvin S, Martinson FE, Kazembe PN, *et al*. **Frequent detection of acute primary HIV infection in men in Malawi.** *AIDS* 2004; **18**:517–524.
33. **Acute HIV infection - New York City, 2008.** *MMWR Morb Mortal Wkly Rep* 2009, **58**:1296–1299.
34. Stekler JD, Swenson PD, Coombs RW, Dragavon J, Thomas KK, Brennan CA, *et al*. **HIV testing in a high-incidence population: is antibody testing alone good enough?** *Clin Infect Dis* 2009; **49**:444–453.

35. Wright AA, Katz IT. **Home testing for HIV.** *N Engl J Med* 2006; **354**:437–440.
36. Branson BM. **Home sample collection tests for HIV infection.** *JAMA* 1998; **280**:1699–1701.
37. Colfax GN, Lehman JS, Bindman AB, Vittinghoff E, Vranizan K, Fleming PL, *et al*. **What happened to home HIV test collection kits? Intent to use kits, actual use, and barriers to use among persons at risk for HIV infection.** *AIDS Care* 2002; **14**:675–682.
38. **Rapid HIV test distribution–United States, 2003–2005.** *MMWR Morb Mortal Wkly Rep* 2006; **55**:673-676.
39. CDC. *CLIA Certificate of Waiver fact sheet*. Available at: http://www.cdc.gov/hiv/topics/testing/resources/factsheets/rolt-clia.htm. [Accessed 16 August 2012].
40. Hutchinson AB, Branson BM, Kim A, Farnham PG. **A meta-analysis of the effectiveness of alternative HIV counseling and testing methods to increase knowledge of HIV status.** *AIDS* 2006; **20**:1597–1604.
41. Cohall A, Dini S, Nye A, Dye B, Neu N, Hyden C. **HIV testing preferences among young men of color who have sex with men.** *Am J Public Health* 2010; **100**:1961–1966.
42. Phillips KA, Chen JL. **Willingness to use instant home HIV tests: data from the California Behavioral Risk Factor Surveillance Survey.** *Am J Prev Med* 2003; **24**:340–348.
43. Gaydos CA, Hsieh YH, Harvey L, Burah A, Won H, Jett-Goheen M, *et al*. **Will patients "opt in" to perform their own rapid HIV test in the emergency department?** *Ann Emerg Med* 2011; **58**:S74–78.
44. Choko AT, Desmond N, Webb EL, Chavula K, Napierala-Mavedzenge S, Gaydos CA, *et al*. **The uptake and accuracy of oral kits for HIV self-testing in high HIV prevalence setting: a cross-sectional feasibility study in Blantyre, Malawi.** *PLoS Med* 2011, **8**:e1001102.
45. Ng OT, Chow A, Lee V, Chen M, Lin L, Chua A, *et al*. **Accuracy and user-acceptability of HIV self-testing using an oral fluid HIV rapid test [Abstract 1075] In: 18th Conference on Retroviruses and Opportunistic Infections.** *Boston, Massachusetts*; 2011.
46. Asia Pacific Foundation of Canada. MedMira Launches Rapid HIV Test in Hong Kong, Macao; 2005. http://www.asiapacific.-ca/fr/news/medmira-launches-rapid-hiv-test-hong-kong-macao. [Accessed 18 August 2012].
47. INTEC; 2012. http://selfdetect.com/en/index.html. [Accessed 16 August 2012].
48. HM Government. The HIV Testing Kits and Services Regulations 1992. http://www.legislation.gov.uk/uksi/1992/460/contents/made. [Accessed 16 August 2012].
49. Commonwealth of Australia. 2011 National HIV Testing Policy. http://testingportal.ashm.org.au/resources/Australian_National_HIV_Testing_Policy_v1-1.pdf. [Accessed 16 August 2012].
50. Food and Drug Administration (FDA). Vital facts about HIV home test kits. http://www.cdc.gov/hiv/topics/testing/rapid/rt-comparison.htm. [Accessed 16 August 2012].
51. BPAC: November 3, 2005. http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4190t1.htm. [Accessed 17 August 2012].
52. BPAC. Transcript of the BPAC 86th Meeting: March 10, 2006. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4206t2.pdf. [Accessed 17 August 2012].
53. OraSure Technologies. OraSure Makes Final FDA Submission for Approval of Over-the-Counter Rapid HIV Test (press release). http://phx.corporate-ir.net/phoenix.zhtml?c=99740&p=irol-corpnewsArticle&ID=1643909&highlight=. [Accessed 18 August 2012].
54. FDA. OraQuick® In-Home HIV Test Summary of Safety and Effectiveness; 2012. http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM312534.pdf. [Accessed 17 August 2012].
55. OraSure Technologies. Final Advisory Committee Briefing Materials: Available for Public Release: OraQuick In-Home HIV Test. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM303652.pdf. [Accessed 18 August 2012].
56. Forshee RA. Model to estimate the public health benefits and risks of the OraQuick In-Home HIV Test kit based on its performance in Phase III trials; 2012. http://fda.yorkcast.com/webcast/Viewer/?peid=ba104b31fe4c4c099568bacda9a4e5401d. [Accessed 17 August 2012].
57. Paltiel AD, Walensky RP. **Home HIV Testing: Good News but Not a Game Changer.** *Ann Intern Med* 2012, *in press*.
58. Mavedzenge Napierala S, Baggaley R, Ru Lo Y, Corbett E. *HIV self-testing among health workers: A review of the literature and discussion of current practices, issues, and options for increasing access of HIV testing in Sub-Saharan Africa*. In. Geneva: World Health Organization (WHO); 2011.
59. Richter M, Venter WD, Gray A. **Home self-testing for HIV: AIDS exceptionalism gone wrong.** *S Afr Med J* 2010; **100**:636–642.
60. Campbell S, Klein R. **Home testing to detect human immunodeficiency virus: boon or bane?** *J Clin Microbiol* 2006; **44**:3473–3476.
61. Marzuk PM, Tierney H, Tardiff K, Gross EM, Morgan EB, Hsu MA, *et al*. **Increased risk of suicide in persons with AIDS.** *JAMA* 1988; **259**:1333–1337.
62. Cote TR, Biggar RJ, Dannenberg AL. **Risk of suicide among persons with AIDS. A national assessment.** *JAMA* 1992; **268**:2066–2068.
63. Dannenberg AL, McNeil JG, Brundage JF, Brookmeyer R. **Suicide and HIV infection. Mortality follow-up of 4147 HIV-seropositive military service applicants.** *JAMA* 1996; **276**:1743–1746.
64. Perry SW, Jacobsberg LB, Fishman B, Weiler PH, Gold JW, Frances AJ. **Psychological responses to serological testing for HIV.** *AIDS* 1990; **4**:145–152.
65. Branson BM. **The future of HIV testing.** *J Acquir Immune Defic Syndr* 2010; **55 (Suppl 2)**:S102–S105.
66. Louie B, Pandori MW, Wong E, Klausner JD, Liska S. **Use of an acute seroconversion panel to evaluate a third-generation enzyme-linked immunoassay for detection of human immunodeficiency virus-specific antibodies relative to multiple other assays.** *J Clin Microbiol* 2006; **44**:1856–1858.
67. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, *et al*. **Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda.** *J Infect Dis* 2005; **191**:1403–1409.
68. Ventuneac A, Carballo-Dieguez A, Leu CS, Levin B, Bauermeister J, Woodman-Maynard E, *et al*. **Use of a rapid HIV home test to screen sexual partners: an evaluation of its possible use and relative risk.** *AIDS Behav* 2009; **13**:731–737.
69. Paltiel AD, Pollack HA. **Price, performance, and the FDA approval process: the example of home HIV testing.** *Med Decis Making* 2010; **30**:217–223.
70. Denning P, DiNenno E. **Communities in crisis: is there a generalized HIV epidemic in impoverished urban areas of the United States?** [Abstract WEPDD101]. In: *XVIII International AIDS Conference*. Vienna, Austria; 2010.
71. An Q, Prejean J, McDavid Harrison K, Fang X. **Association Between Community Socioeconomic Position and HIV Diagnosis Rate Among Adults and Adolescents in the United States 2005 to 2009.** *Am J Public Health* 2013; **103**:120–126.
72. de la Fuente L, Rosales-Statkus ME, Hoyos J, Pulido J, Santos S, Bravo MJ, *et al*. **Are Participants in a Street-Based HIV Testing Program Able to Perform Their Own Rapid Test and Interpret the Results?** *PLoS One* 2012; **7**:e46555.
73. Katz DA, Golden MR, Stekler JD. **Use of a home-use test to diagnose HIV infection in a sex partner: a case report.** *BMC Res Notes* 2012; **5**:440.
74. Gray R, Kigozi G, Kong X, Ssempiija V, Makumbi F, Wattya S, *et al*. **The effectiveness of male circumcision for HIV prevention and effects on risk behaviors in a post-trial follow up study in Rakai, Uganda.** *AIDS* 2012; **26**:609–615.
75. Sonder GJ, Prins JM, Regez RM, Brinkman K, Mulder JW, Veenstra J, *et al*. **Comparison of two HIV postexposure prophylaxis regimens among men who have sex with men in Amsterdam: adverse effects do not influence compliance.** *Sex Transm Dis* 2010; **37**:681–686.
76. Colfax GN, Buchbinder SP, Cornelisse PG, Vittinghoff E, Mayer K, Celum C. **Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion.** *AIDS* 2002; **16**:1529–1535.
77. National Institutes of Health (NIH). **Home Self-Testing for HIV to Increase HIV Testing Frequency in Men Who Have Sex With Men (The iTest Study).** In: *ClinicalTrials.gov website*; 2011. http://clinicaltrials.gov/ct2/show/

NCT01161446?term=NCT01161446&rank=1. [Accessed 18 August 2012].
78. Sharma A, Sullivan PS, Khosropour CM. **Willingness to Take a Free Home HIV Test and Associated Factors among Internet-Using Men Who Have Sex with Men.** *J Int Assoc Physicians AIDS Care (Chic)* 2011; **10**:357–364.
79. Wayal S, Llewellyn C, Smith H, Fisher M. **Home sampling kits for sexually transmitted infections: preferences and concerns of men who have sex with men.** *Cult Health Sex* 2011; **13**:343–353.
80. Kimbrough LW, Fisher HE, Jones KT, Johnson W, Thadiparthi S, Dooley S. **Accessing social networks with high rates of undiagnosed HIV infection: The social networks demonstration project.** *Am J Public Health* 2009; **99**:1093–1099.
81. Spielberg F, Levine RO, Weaver M. **Self-testing for HIV: a new option for HIV prevention?** *Lancet Infect Dis* 2004; **4**:640–646.
82. National AIDS and STI Control Programme. **Guidelines for HIV Testing and Counselling and Kenya.** In. *Nairobi: Ministry of Public Health and Sanitation, Kenya*; 2010.
83. Campsmith ML, Rhodes PH, Hall HI, Green TA. **Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006.** *J Acquir Immune Defic Syndr* 2010; **53**:619–624.
84. Rosenberg NE, Kamanga G, Phiri S, Nsona D, Pettifor A, Rutstein SE, *et al*. **Detection of acute HIV infection: a field evaluation of the determine(R) HIV-1/2 Ag/Ab combo test.** *J Infect Dis* 2012; **205**:528–534.