The Current CLIA Waiver Process and HIV Testing
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More Cost than Benefit?

Summation of Oral Comments (with References) of:
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*The Author hereby declares he has no known financial interests in any of the issues discussed in these comments.

[START]

Good day. My name is James Krellenstein, and I am here representing ACT UP\New York, a New York City based HIV\AIDS activist group. My trip here and accommodation in Atlanta was provided through Treatment Action Group (TAG), an AIDS, TB and Hepatitis C think-tank. In addition to my work with ACT UP, I am also a student studying physics at The City College of New York.

Today, I would like to discuss what I think are some of the unintended consequences of the current CLIA waiver process when applied to the evaluation of new HIV rapid tests.

I. Some Background on the Importance of Rapid HIV Testing in Non-Clinical and Point of Care Settings

One of the most important objectives of both HIV treatment and prevention programs is to make sure that people living with HIV infection are *actually* diagnosed and linked to medical care. The ability to test for HIV infection in non-clinical setting--for example, in gay bars, parks, parades etc.--is essential to diagnosing persons who are at risk for HIV infection, but do not normally access primary care. The importance of this becomes even more apparent when one considers the characteristics of some of the population groups at highest risk for HIV infection, like young gay and bisexual men.

Even for persons who routinely access primary care, rapid tests allow patients to receive the results of the test in minutes, rather than days, while still at the point of care, significantly minimizing the probability of loss to follow up[1].

In addition to the obvious importance of diagnosis for the health of persons living with HIV, it is also essential to HIV prevention. A 2012 study estimated that undiagnosed persons living with HIV were the source of approximately 50% of forward transmissions, despite representing only 20% of persons living with HIV.[2] Indeed, a recent CDC analysis of HIV prevention strategies indicated that non-clinical HIV testing is the single most cost effective intervention in terms of cost per new infection averted.[3]

Furthermore, the use of HIV Post Exposure Prophalaxis (PEP) and Pre-Exposure Prophylaxis (PrEP) requires that prescribers definitively rule out the possibility of existing HIV infection before initiating therapy.

II. Rapid HIV Tests Must be CLIA Waived in order to be performed in Non-Clinical Settings and most Point of Care Settings.

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1 *e.g.* Pant Pai N, Peeling RW, Smith BD. Dowdy D. Point-of-care tests for HIV, related coinfections, and blood-borne infections. *AIDS Research and Treatment.* 2014

2 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(7):893-6.

3 Samson SL. "Modeling to Identify Optimal Allocation of HIV Prevention Resources in a City Health Department".(Slide 37) Presented at: *CDC Grand Rounds*, Atlanta, Georgia, 21 August 2012. URL: http://www.cdc.gov/cdcgrandrounds/pdf/gr-hiv-8-21.pdf

In order for any organization to perform rapid tests in the non-clinical setting, they must themselves posses a CLIA Certificate of Waiver or be affiliated with a CLIA waived laboratory.[4] As we all are aware, only tests that have been granted a CLIA Waiver by the Food and Drug Administration (FDA) can be used in CLIA waived settings.

III. All current CLIA waived Rapid Tests are Second Generation HIV Tests

While the FDA has granted CLIA Waivers to more than 7 HIV rapid tests since 2002[5], all of these HIV tests are so-called "second generation" HIV tests. Second generation HIV tests can only detect anti-HIV antibodies of the immunoglobulin G (IgG) isotype and are unable to detect the presence of either immunoglobulin M (IgM) anti-HIV antibodies or antigenic components of the virus itself. This results in second-generation HIV tests misdiagnosing many recently infected HIV positive patients—i.e. patients in "acute infection"--as HIV negative.

For example, a 2008 study performed in New York City found that 9% of all HIV positive persons identified in four STD clinics were misdiagnosed as HIV negative by a CLIA waived second-generation rapid test because the patients were in acute HIV infection.[6]

Not only is the misdiagnosis of HIV infection in patients in acute HIV infection detrimental to the health of persons misdiagnosed, it also has significant public health implications. Despite the short duration of acute infection, acutely infected patients are estimated to be the source of approximately 40% to 50% of forward transmissions.[7] [8]

IV. The Current CLIA Waiver Process is Preventing More Accurate HIV Tests from being used in Non-Clinical and Point of Care Settings.

On August 9, 2013 the FDA approved a new rapid HIV test, the Alere Determine™ HIV-1/2 Ag/Ab Combo, which can detect *both* anti-HIV IgG and IgM antibodies, as well as directly detecting HIV p24 antigen (i.e. a "fourth-generation" HIV test).[9] Published data indicates that the Determine test is far superior to existing 2nd

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4 Centers for Disease Control and Prevention. "CLIA Certificate of Waiver Fact Sheet" URL: http://www.cdc.gov/hiv/testing/lab/clia/

5 Food and Drug Administration. "CLIA - Clinical Laboratory Improvement Amendments - Currently Waived Analytes." URL: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfclia/analyteswaived.cfm

6 CW Shepard et al. "Acute HIV Infection --- New York City, 2008." *MMWR*.2009;58(46):1296-1299

7 Brenner BG et al. "High rates of forward transmission events after acute/early HIV-1 infection." *J Infect Dis*. 2007;195(7):951-9

8 Volz EM et al. "HIV-1 transmission during early infection in men who have sex with men: A phylodynamic analysis." *PLoS Medicine*. 2013;10(12):1-12

9 US FDA. "August 9, 2013 Approval Letter - Alere Determine HIV-1/2 Ag/Ab Combo". URL: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm364653.htm

generation HIV rapid tests in correctly diagnosing patients undergoing acute HIV infection.[10]

Yet despite being procedurally identical to existing CLIA waived HIV rapid tests, the FDA automatically classified the Determine Test as "moderate complexity" under CLIA; preventing all non-clinical and CLIA waived testing sites from using the Determine test, and forcing them to rely on older, less accurate second generation HIV tests. This has undoubtedly resulted in numerous HIV positive persons being misdiagnosed as HIV negative, with significant negative implications for both the individual health of these patients and the public health of communities affected by this epidemic.

While Alere has submitted an application to the FDA for CLIA waiver, as of today—more than a year since the approval of the test--it has yet to grant it. In this time, the CDC estimates that more than 50,000 Americans became newly infected with HIV.

V. Conclusions

I urge this committee to consider the unintended consequences of the current CLIA wavier process, especially when it comes to evaluating new HIV diagnostics. I understand the necessity of closely regulating medical tests that are going to be performed primarily by untrained personnel. But implicit in any government regulation are *both* costs and benefits. It is pretty hard, in the case of the Determine Test, to see how the real costs of this policy (i.e. forcing HIV testing campaign to use older, less accurate tests) are outweighed by the benefits, if any. I urge the committee to consider ways of ensuring that only appropriate tests are CLIA waived, while minimizing the public and individual health costs of this policy. This is especially important as newer HIV testing modalities, like point of care nucleic acid amplification tests, are developed and brought to market.

Thank you.

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[10] Masciotra S, et al. "Performance of the Alere Determine™ HIV-1/2 Ag/Ab combo rapid test with specimens from HIV-1 seroconverters from the US and HIV-2 infected individuals from Ivory Coast." *Journal of Clinical Virology.* 2013;58(SUPPL1):e54-8.