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Maximizing the Delivery Performance of Point- of-Care CD4⁺ T-Cell Counting Tests in Resource-Limited Settings – A Policy Brief

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Abstract

Managing HIV/AIDS presents challenges to public health policymakers, frontline workers, and researchers worldwide. A key strategy in the disease management is early diagnosis and rapid treatment initiation. While the technological field of point-of-care HIV/AIDS diagnostics has advanced significantly in the past two decades, several critical issues remain that hinder the deployment of point-of-care testing devices in resource-deprived settings. In this policy brief, we discuss these issues, including technological specifics of point-of-care CD4⁺ T-cell counting approaches and requirements of deploying them. We also discuss cultural and religious concerns on the deployment. At the end of the brief, we propose a roadmap for the efficient and cost-effective deployment and call for action to assemble multidisciplinary teams for the undertaking. We argue that joint effort must be taken to conduct research and development for low-cost portable point-of-care testing and for tailoring the technology deployment and care delivery support system design for specific cohorts.

Important Policy Issues Related to Point-of-Care (POC) Diagnostics for HIV

Early diagnosis and rapid initiation of treatment remains a key strategy to managing HIV/AIDS, which is still an important public health problem worldwide. Low-cost portable POC tests have shown great promise of completely transforming the management (Yager et al. 2008), especially in resource-limited settings where healthcare infrastructure is weak and the access to quality and timely care is a challenge. These tests offer rapid results at or near the site of patient care, which allows for rapid initiation of appropriate treatment and/or establishment of linkages to care (Peeling and Mabey 2010). More importantly, POC tests can be simple enough to be used not only at conventional settings but also in settings with no laboratory infrastructure. POC tests are often more cost-effective for the healthcare delivery system (Peeling and Mabey 2010), and can potentially empower patients to self-testing with privacy and make informed decisions on their own.

Clinicians, researchers, and public health staff who work at the frontline of HIV/AIDS care and control have had access to an outstanding array of POC devices at their hospital. However, great challenges remain in deploying

these devices in an efficient and cost-effective manner by considering the socioeconomic status of certain resource-deprived regions, as well as cultural and religious factors in the regions. To resolve these challenges, there is an urgent need for assembling a multidisciplinary team of experts in the domains of bio-sensing, operations research, public health, global policy, sociology, and religious studies. The joint effort must be made to answer the following policy questions related to diagnostics and treatment monitoring, which helps improve the delivery of needed care globally:

- a. **Technology Research & Development Investment.** Along which direction we can receive a higher return socioeconomically, between investing on AIDS medical research to improve current treatments (e.g., vaccine development as well as side effect reduction and adherence improvement of current drugs) and investing on testing deployment technology and systems research to improve current disease management in resource-limited settings (e.g., POC testing development to aid in HIV diagnosis, disease staging, and treatment monitoring of HIV/AIDS).
- b. **Technology Deployment Research and Care Delivery Support System Design.** What POC HIV testing approaches can be extended for addressing the specific needs in resource-limited settings (e.g., antibody, antigen, nucleic acid-based, CD4 count, etc.)? What are the necessary system requirements for efficient and cost-effective deployment of the selected tests?
- c. **Social, Cultural, and Religious Studies for Technology Deployment.** What is an appropriate human right approach applied to POC HIV testing that pays due respect to ethical principles? How to alleviate the social stigma and misconceptions so that the testing technology can be better deployed and the care delivery support system can be more effectively implemented?

The remainder of this policy brief is organized as follows. In Section 2, we introduce the background of HIV/AIDS to understand the current state of HIV/AIDS care and management, and motivate the needs for developing and deploying POC test methods. In Section 3, we focus on a discussion of the commercially available CD4 T-cell counting technologies and the roadblocks of

deploying them efficiently and cost-effectively in resource-limited settings. In Section 4, we propose a roadmap for the success and call for multidisciplinary efforts to tackle the above policy questions.

Background of HIV/AIDS

Human immunodeficiency virus infection/ Acquired immunodeficiency syndrome (HIV/AIDS), a disease of human immune system, is caused by the human immunodeficiency virus (HIV) (Sepkowitz 2001; Fauci 2008). After HIV is in the body, it attacks and destroys CD4⁺ T-cells, which are the part in the immune system that fights infection and diseases. The primary causes of HIV transmission are sexual contact and blood transfusion. In addition, a person can be infected through the sharing of dirty needles. A child can also get HIV from the mother during pregnancy, delivery, or breastfeeding (Rom and Markowitz 2007, p. 745). Once a person is infected, there are three main stages of HIV infection: initial infection, clinical latency, and AIDS (Mandell et al. 2010, Chapter 121; US DHHS 2010). Following the contraction of HIV, a person may experience a brief period of influenza-like illness (Cavendish 2008, p. 25; Mandell et al. 2010, Chapter 118). This is typically followed by a prolonged period (i.e., 3 – 20 years and 8 years on average) without symptoms (Evian 2006, p. 29; Hicks 2006, p. 19; Elliot et al. 2012, p. 273). While there are typically few or no symptoms at first, many people experience fever, weight loss, gastrointestinal problems, and muscle pains near the end of this stage (US DHHS 2010). In the absence of treatment, around half the people with HIV will develop AIDS within 10 years (Mandell et al. 2010, Chapter 118).

AIDS is considered a global pandemic -- a disease outbreak that is present and actively spreading worldwide (Kallings 2008). It is a great public health challenge worldwide with significant socioeconomic impacts, as well as noticeable cultural and religious consequences. Prevention of HIV infection, primarily through safe sex and needle-exchange programs, is a key strategy to control the spread of HIV/AIDS (Crosby and Bounse 2012). Meanwhile, even though there is no cure or effective HIV vaccine, antiretroviral treatment has been shown to be effective in

slowing the disease progression, which may result in a near-normal life expectancy (May and Ingle 2011). As of 2010, more than 6.6 million people were receiving antiretroviral treatment in low and middle income countries (USAIDS 2011, pp. 1 - 10). Unfortunately, antiretroviral treatment medications are expensive (Orsi and d'almeida 2010) and may be associated with side effects (Montessori et al. 2004). Hence it is critical to determine the timing of treatment initiation, especially in resource-deprived areas. To make intelligent decisions at the individual patient level, it is important to have accurate CD4⁺ T-cell counts. A collection of accurate test results will also lead to accurate modeling of disease progression and in turn intelligent development and modification of deployment policies and clinical guidelines in resource-limited settings.

Epidemiology

As a disease, HIV/AIDS has threatened, if not devastated, many societies. It has led to nearly 30 million deaths between recognizing it the first time in 1981 and 2009 (USAID 2010). As of 2010, approximately 34 million people worldwide have contracted HIV (USAIDS 2011, pp. 1-10). Of these, approximately 16.8 million are women and 3.4 million are younger than 15 years old (USAIDS 2011, pp. 1-10). It resulted in about 1.8 million deaths in 2010 (USAIDS 2011, pp. 1-10).

Sub-Saharan Africa is the region that is most affected by HIV/AIDS. In 2010, an estimated nearly 25 million people lived with HIV in this region, which constitute of more than two thirds of the HIV cases globally (USAIDS 2011, pp. 20-30). Approximately, 1.2 million (or 66% of worldwide) deaths occurred in the region (USAIDS 2011, pp. 20-30), which is equivalent to roughly 5% of the adult population in the region (USAIDS 2011, pp. 40-50). In contrast to other regions with high AIDS prevalence, women comprise a large portion of the deaths (nearly 60%) in sub-Saharan Africa (USAIDS 2011, pp. 20 -- 30). It is also believed that 10% of all deaths among children were caused by HIV/AIDS. In addition, 14.8 million children have lost their parents to HIV/AIDS, accounting for almost 90% of the children orphaned by AIDS worldwide. South Africa has the largest HIV infected population in any country. Life expectancy has fallen in the worst-affected countries due to

HIV/AIDS; for example, it was estimated in 2006 that the life expectancy in Botswana had dropped from 65 in the early 1980's to 35 years (Kallings 2008).

South and Southeast Asia is the second most affected, accounting for 4 million cases (or 12% of all people living with HIV) in 2010 and approximately a quarter million people died from HIV in the same year (USAIDS 2011, pp. 40-50). Even though AIDS has received great attention in the United State, its prevalence is still noticeable. In 2008, 1.2 million people in the United States lived with HIV, resulting in about 17,500 deaths (CDC 2011).

Socioeconomic Impacts

HIV/AIDS affects the economies of both individuals and countries (Bell et al. 2003; Mandell et al. 2010, Chapter 117). The forecast is that it will probably cause the collapse of economies and societies in countries with a significant AIDS population. First, it affects the economic growth by reducing the availability of human capital (Bell et al. 2003; Mandell et al. 2010, Chapter 117). Without proper nutrition and necessary medicine care, large numbers of young people in many developing countries are falling victim to AIDS. They are not only unable to work, but also require significant medical care. The increased mortality leads to a reduced skill worker population, which in turns presents pressure on the country's finance and derails its economy growth (Greener 2002). HIV/AIDS also weakens the mechanism that generates human capital, due to increased spending on medical care and death of parents with HIV/AIDS. The households that lose the parents will have less income to spend on education and other personal or family investment (Over 1992). In many heavily infected regions, AIDS has left behind many orphans (Greener 2002; Mandell et al. 2010, Chapter 117).

In summary, much emphasis has been given in the past twenty years to the development of effective HIV/AIDS treatments. The current treatments are shown to be effective given timely disease staging and close treatment monitoring. However, these prerequisites are difficult to realize in resource-limited settings. This explains why low-cost, portable, wireless-enabled, easy-to-use POC testing is needed.

Cultural and Religious Factors

There are many misconceptions about HIV/AIDS such as the belief that it can be transmitted by casual non-sexual contact (Sowadsky 1997). Other common misconceptions include that AIDS can be cured by sexual intercourse with a virgin (Flanagan 2001) and that HIV can infect only homosexual men and drug users (CDC 2008). These misconceptions lead to social stigma around the world to HIV/AIDS patients, which is a significant contributing factor for ineffective HIV/AIDS care (Pharris et al. 2011). A misconception directly related to CD4⁺ T-cell counting is the belief that only a small number of CD4⁺ T-cells are infected by HIV, not enough to damage the immune system (Richman 2000).

The stigma exist in a variety of ways, including ostracism, rejection, discrimination, and avoidance of HIV infected people; compulsory HIV testing without prior consent or protection of confidentiality; violence against HIV infected individuals or people who are perceived to be infected with HIV; and the quarantine of HIV infected people (USAID 2006). Stigma-related violence or the fear of violence prevents many people from seeking HIV testing, returning from their results, or securing treatment, possibly turning what could be a manageable chronic illness into a death sentence and perpetuating the spread of HIV (Ogden and Nyblade 2005). A recent study has found that as many as 40% of Americans who are HIV-positive do not begin a care regimen within the first 6 months after diagnosis (Mugavero 2008).

The disease has also become subject to many controversies involving religious beliefs (Mandel 2011, Kerr 2012). A group of people and organizations continue to deny the causality between HIV and AIDS (Duesberg 1988). Some other forms of denial include rejecting the existence of HIV itself, or the validity of HIV testing and treatment methods (Smith and Novella 2007; Kalichman 2009). These denials, known as AIDS denialism (Kalichman 2009, p. 205), have incurred great human cost as they discourage HIV-positive people from using proven treatments (Cohen 1994; Watson 2006; Smith and Novella 2007). In addition, AIDS denialism has had a significant political impact, especially in South Africa where the HIV/AIDS prevalence is alarmingly high (Chigwedere et al. 1999). Meanwhile, it is

important to point out that many faith-based organizations or churches have established social service and caring centers for HIV/AIDS patients, and the religious community could be mobilized to provide awareness education and technological dissemination.

In summary, POC testing is expected to help empower patients to make informed decisions through convenient testing with privacy and thus alleviate the difficulties arising from the aforementioned social stigma, cultural misconceptions, and religious concerns. On the other hand, the aforementioned concerns demand serious considerations when developing POC HIV testing technology and designing the associated care management information system, e.g., on the issue of information security. Finally, the social support provided by religious organizations is undeniable and should be taken into consideration when investigating the human factors in deploying POC HIV testing technology.

CD4 T-Cell Counting and Antiretroviral Therapy

Many different tests are used in HIV diagnosis, disease staging, and treatment initiation. As HIV/AIDS has become a chronic rather than an acutely fatal disease in many areas of the world (Knoll 2007), it becomes critical to monitor the immune system functionality among HIV-positive people and inform them with treatment decisions (e.g., initiation of antiretroviral therapy). Similar to a white blood cell count to determine infection, certain biomarkers help a clinician determine the status of an individual's HIV status. These biomarkers are the T-cell lymphocytes. A normal CD4 count varies between 500 and 1500 cells per microliter in blood (WHO 2007, pp. 6-16). Declining CD4 counts are considered to be a sign of progression of HIV infection (WHO 2007, pp. 6-16). Among HIV-positive people, AIDS is officially diagnosed when the count drops below 200 per microliter based on the CDC classification (CDC 2008).

When to start antiretroviral therapy is subject to debate (Sax and Baden 2009). If antiretroviral therapy is administered too early, it may not lead to any improvement and this costly medicine is wasted. In addition, antiretroviral therapy may hinder a healthy individual's natural immune

system. If it is administered too late, i.e., after the CD4 count drops below 50 per microliter, patients in general cannot be saved. A guideline developed by the U.S. Centers for Disease Control identifies persons with CD4 counts less than 200 per microliter as having AIDS (<http://www.cdc.gov/hiv/resources/guidelines/>). Once CD4 count is below 200, antiretroviral treatment is necessary for patient's survival. It is also believed that beginning treatment at the level of 350 can reduce the risk of death (WHO 2010, pp. 19-20). Furthermore, CD4 count is needed to determine the appropriateness of treatment regimen given. Therefore, it is important to receive accurate and timely CD4 counts for HIV-positive patients.

Flow cytometry is the primary means for CD4⁺ T-cell counting. In the 40 years since the invention of the cell sorter (Fulwyler 1965), a revolution has occurred within the world of immunology primarily driven by innovations of Len Herzenberg (Herzenberg et al., 1977; Loken and Herzenberg, L. A., 1975; Roederer et al., 1997) and others as cytometry matured into a powerful technology in medical research and clinical practice. However, a flow cytometer remains a precision instrument at present. First, it is costly, e.g., a typical flow cytometer costs USD \$50,000 to \$100,000. Second, it must be used by a trained operator and is meant to be installed in a lab in a stationary location. Finally, its power requirement necessitates highly controlled settings. As a result, POC flow cytometers have emerged as the next generation HIV/AIDS diagnostic and treatment monitoring devices, especially in resource-limited settings. In the next section, we discuss the needs and gaps of the current systems and approaches.

POC CD4 T-Cell Counting Technology: Needs and Gaps

Clinicians, researchers, and public health staff who work at the frontlines of HIV care and control have had access to an outstanding array of POC diagnostics at their disposal, although uptake of these tests has varied across countries. POC tests for HIV include those used for screening, initial diagnosis, disease staging, treatment monitoring, and early infant diagnosis. An excellent survey of the current HIV diagnostics landscape has been published recently (Murtagh, 2011).

Between 30 and 40 million people in resource-

deprived regions infected with the HIV virus need antiretroviral treatment. Two barriers exist. First, the cost is high; many efforts are at work to reduce these costs. Second, to receive therapy, each individual's CD4 level must be monitored. Point-of-care testing increases the likelihood of receiving the results quickly and making immediate treatment initiation decisions. The field of POC testing for CD4 count has advanced to consider over-the-counter, self-testing options and the use of multiplexed platforms that allow for simultaneous detection of infections associated with HIV, such as hepatitis B and C, and syphilis.

Unfortunately, flow cytometry is complex and expensive in today's technology-focused world. While next-generation ideas are important, they are not the solution for the present challenges on HIV/AIDS patient evaluation for CD4 levels in resource-limited settings. Cytometers can and must be made inexpensively to deal with the global HIV/AIDS crisis. Furthermore, POC testing is often accomplished through the use of transportable, portable, and handheld instruments and test kits. In remote villages, some NGOs have begun transporting blood samples to and from central hospitals to determine the CD4 count. This can take weeks. Travel and testing is made more complex by the testing cycle in high-volume hospitals, which can take hours or days. These processes also fail to provide a link between HIV determination, CD4 therapeutic qualification and therapy administration. With small handheld devices that can be used in rural and remote areas, patients in a matter of minutes can get confirmatory testing, obtain their CD4 count and, if qualified, receive immediate antiretroviral treatment. There are several moderately low cost systems available today (several sample systems are listed below). However, these systems are still intended for use in western countries and do not fit well in resource-limited settings.

- **Pointcare** (<http://www.pointcare.net>) has developed small instruments that are well suited for small hospitals. They do not have any communication tools or technologies integrated and rely on an attached computer for computation and communication.
- **Partec** (<http://www.partec.com>) has developed a large range of moderately low cost instruments, including a recent addition of an

entirely portable instrument (around \$14,000), which is battery operated and can achieve many of the needs in resource-limited settings.

- **Millipore** (<http://www.millipore.com>) has developed a product called Millipore Muse, which is a low cost instrument (\$12,000) that has the capacity for CD4 count in resource-limited settings. This small lightweight instrument can be operated on a car battery for short periods of time.
- **Becton Dickinson** (<http://www.bd.com>) has a product called the FacsCount, which is the primary instrument currently used in Africa. However, it is neither small nor light (80 lbs), and its cost is high (\$35,000).
- **Zyomyx** (<http://www.zyomyx.com>) has a product that uses visual readout using a low cost testing device. However, it is not clear if this technology will be accurate and robust. Further, the cost of individual tests may be significantly higher than affordable. It does not have electronic readout or ability to transmit data points.

From the above discussion, we identify the following important features for the next-generation CD4 cell-counting tools. In addition to such features as *low-cost* and *portable*, which are essential to resource-deprived geographically vast areas, these tools must be:

- **Robust.** It is often harsh environment weather-wise in these resource-deprived regions (e.g. in sub-Saharan Africa).
- **Field-operated.** Health providers may not have a skill set equivalent to their counterparts in industrialized countries; laboratories may not be equipped as well as their counterparts either.
- **Batter-operated.** Many households in these resource-deprived regions may not have electricity.
- **Equipped with secured GPS and cell-phone technology.** Testing results can be managed with sufficient security measure in a centralized fashion, which enables epidemiological studies that are beneficial to HIV/AIDS public health policy development.

Furthermore, an overall system solution for supporting the care delivery must be sought by local health care providers in order to have the

ability to decentralize these testing tools, keeping pace with the testing and therapeutically advances for HIV/AIDS. For example, a fundamental problem is the lack of ability to integrate communication and tracking tools with current instruments. There is a need to investigate, at the highest level, whether inclusion of such tools will be a necessary step before the problem of access to resource-limited countries will be overcome. This means more organized management, cloud architecture, cell phone linkages, and better relationships between manufacturers and CDC, Clinton Foundation, Gates Foundation, WHO, etc. It also means manufacturers need to develop more standards that allow data comparison, transmission, and management.

A Proposal of POC CD4 Cell Counting Technology Deployment

An ideal instrument should have the following detailed technological features: 1) it must be small, portable, low cost (<\$5000) so as to lower the per test cost to below \$2; 2) it should provide accurate simple readout with CD4 count, and percentage of total lymphocytes; 3) it should use fingerprick for sampling not venipuncture; 4) it should deliver testing location (GPS) to cell phone devices with coordinated central data collection service; 5) it should demand minimal training for accurate use by each individual or a field care provider; 6) it should be repairable within geographic location of use (or swapped out with new device); and 7) it can last a minimum of 8 hours on rechargeable battery or hand driven generator. To deploy the proposed instruments efficiently and cost-effectively, a system equipped with public cloud computing technology must be designed. Such a system must be secure, user-friendly, as well as culturally and religiously conscious.

To ensure the feasibility in the research and development of the proposed technology and system solution, multidisciplinary teams must be assembled to investigate the policy questions of interest for specific regions with clear understanding of epidemiological and economic factors in the regions. The team must consist of experts in bio-sensing, database technology, cloud computing technology, operations research, public health and international affairs. Proof-of-concept studies in a laboratory environment (e.g. agent-based simulation) must be carried out before field

studies. Field studies must be carried out progressively with consideration of the political environment in each studied region.

With the necessary technological features, the POC are positioned to be the only potential solution to providing low cost diagnostics to mitigate the devastating results of AIDS in resource-deprived regions. With smart e-health system solutions and comprehensive feasibility testing, these tools are anticipated to create a successful relief to the global HIV/AIDS challenge.

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