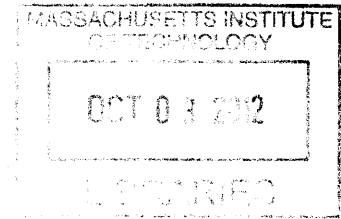**Economic Potential of a Point-of-Care CD4+ T Cell Count Diagnostic in Mexico: A Case Study for Low-End Disruption Diagnostics in Middle of the Pyramid Latin America**

by

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MBA, Harvard Business School, 2011
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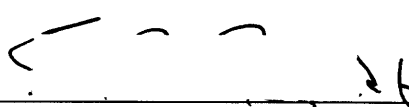
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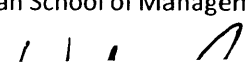
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Economic Potential of a Point-of-Care CD4+ T Cell Count Diagnostic in Mexico. A Case Study for Low-End Disruption Diagnostics in Middle of the Pyramid Latin America

by

Mauricio Camargo Támara

Submitted to the Health Sciences and Technology Program on August 30, 2012 in Partial Fulfillment of the requirements for the Degree of Master of Science in Health Sciences and Technology at the Massachusetts Institute of Technology

Abstract

Disruptive models of innovation are starting to appear in healthcare. In the US, for instance, retail medicine clinics are changing the way in which patients satisfy their basic medical needs. In Mexico, similar retail medicine models (e.g. *Farmacias Similares*) are also disrupting healthcare delivery for basic medical needs. Disruptive innovations, however, are not limited to healthcare delivery, but also change the face of devices and diagnostics markets.

A low CD4+ T cell count is the primary clinical indicator for HIV/AIDS disease progression, and thus is used as the primary trigger to initiate antiretroviral therapy. An entire diagnostic industry has emerged around CD4+ T cell counts for the management and treatment of HIV/AIDS patients. The diagnostic gold standards of CD4+ counts are flow cytometers. These large, capital intensive devices are commonly located in central laboratory settings, typically in urban areas. In developing nations, particularly, suburban and rural regions have no access to flow cytometers and typically face logistical problems of blood sample transportation and loss to follow-up of patients.

Point-of-Care (POC) diagnostics promise disruptive models in diagnostics that will increase access, enhance care, and help better allocate healthcare resources. The concept of POC embodies the trade-off of lower "quality" (usually in the form of lower specificity and sensitivity) in exchange for higher "convenience" (i.e. better accessibility and portability, and significantly lower cost). POC diagnostics promise typical low-end and new-market disruptions in medical diagnostics and devices.

Cambridge-based Daktari Diagnostics is one of such companies focused in POC diagnostics. It has developed a CD4+ T cell count diagnostic device for the management and treatment of HIV/AIDS patients.

It is hypothesized in this thesis that there exists a relevant unmet medical need for POC CD4 count diagnostics in the Mexican HIV/AIDS market. In order to evaluate this hypothesis, secondary sources were reviewed, as well as primary interviews conducted across the Mexican HIV/AIDS healthcare landscape. While this hypothesis was evaluated on a preliminary basis only, responses suggested a relevant, albeit not urgent, medical need for POC CD4 count diagnostics.

This primary hypothesis evaluation is extended by and complemented with market size estimations, and competitive dynamic discussions, that arrive at the following preliminary conclusions: the current market opportunity in Mexico ranges from baseline of ~100,000 tests per year to an upper bound potential of ~200,000 tests per year. In the context of this potential opportunity, Daktari's CD4 count diagnostic device is well positioned, as defined by diagnostic quality, technological characteristics, and competitive offering, to obtain a portion of this estimated market opportunity in Mexico.

Thesis Supervisor: Ernst Berndt, PhD
Thesis Supervisor: William Rodriguez, MD

Dedication

To my grandfather, Dr. Amiro Támara, for being the guide and example that inspired me to pursue a career in healthcare.

To my parents, Otto and Vivianne, for providing me with unbounded opportunities, and to Dina, for her constant love and support.

To my professors and advisors at HST, for lending me the support and energy that made my journey here an enjoyable and fruitful one.

Acknowledgments

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Chapter 1: Introduction

The enormous medical and social burden of AIDS has led to an explosion of research aimed at deciphering HIV and its ability to sidestep and destroy host defenses. Tied to basic scientific research are clinical efforts targeted towards adequately diagnosing, managing and treating patients with HIV/AIDS. There is currently no cure or vaccine for HIV/AIDS. However the development of highly active antiretroviral therapies in the past two decades has drastically changed the prognosis of HIV/AIDS, by delaying immunosuppression and extending patients' lives.

CD4+ T cells counts are the primary clinical indicators of disease progression, and thus are used as triggers for the initiation of antiretroviral therapy. Therefore, an entire diagnostic industry has emerged around CD4+ T cell counts for the management and treatment of HIV/AIDS patients.

The diagnostic gold standards of CD4+ counts are flow cytometers. These large, capital intensive devices are commonly located in central laboratory settings, typically in urban areas. This is particularly the case in developing nations with limited resources, where suburban and rural regions have no access to flow cytometers and typically face logistical problems of blood sample transportation and loss to follow-up and care of patients.

Following what appears to be a traditional low-end disruption model, a new family of CD4+ count diagnostics is starting to emerge. These new diagnostics offer fast and reliable tests at the patient's *point-of-care* (POC), and they do so at an economic advantage and without the need for vein puncturing for sample collection. The trade-off these devices offer is, in essence, lower sensitivity and specificity, but providing a portable, faster, more convenient, and more economical diagnosis. While technological advancements have been made in many fronts, the current POC alternatives are technologically and commercially led by three devices: Alere's Pima, Daktari Diagnostics' Daktari CD4, and mBio's SnapCount.

Daktari CD4, in particular, is at the core of this thesis discussion. The main objective of this thesis is to identify and discuss the unmet medical need for POC CD4 count diagnostics in the Mexican HIV/AIDS market, and to complement this discussion with the estimation of the market potential and commercial feasibility of POC CD4 count diagnostics in general, and

Daktari CD4 in particular. Daktari CD4 is also taken as a representative POC technology that guides further discussion in POC diagnostics in Mexico. The main sources of data and information for the mentioned topics of discussion are both secondary literary sources, as well as primary interviews conducted early in 2012 in relevant stakeholder organizations in the Mexican healthcare systems and in particular in its HIV/AIDS landscape.

The thesis is thus organized as follows. First, a comprehensive overview and background material is discussed, including topics such as the pathogenesis of HIV/AIDS, the disruptive theory of innovation, point-of-care diagnostics in HIV/AIDS, the Mexican healthcare system, and the landscape of HIV/AIDS in Mexico.

This is followed by the evaluation of the first thesis hypothesis: there exists an unmet medical need for POC CD4 T cell count diagnostics in the Mexican HIV/AIDS market, for which POC CD4 count diagnostics, like Daktari CD4, offer a solution. For this evaluation I conduct a review of the Mexican treatment standards, and the typical HIV/AIDS patient experience. This is followed by the identification of three major segments of need, and finished with a cost-benefit illustration of POC CD4 count devices vis-à-vis the otherwise standard treatment.

Next, the second thesis hypothesis is assessed: given the identified unmet medical need, there is a relevant economic potential for POC CD4 count devices, in which the Daktari CD4 device is a commercially viable alternative. Among the areas covered in this section are total market size estimations, sensitivities of market potential factors, and key considerations regarding competitive forces, comparative advantages, and market positioning.

Finally, this thesis is concluded by a synthesis of the trends and opportunities on the one side, and of the lessons and limitations emerging from this analysis on the other.

Chapter 2: Background

As a preface to discussing the core questions of this thesis, I believe it is important to conduct a thorough review of contextual material. The present background chapter introduces some of the areas that I deem necessary to understand so as to adequately dissect the primary thesis hypotheses. The diverse set of topics in this section includes a biological and pathophysiological review of HIV/AIDS, an introduction to the disruptive theory of innovation, a discussion on *Point-of-Care* diagnostics and their use in managing and treating HIV/AIDS, a detailed overview of the Mexican healthcare system, and finally a review of the HIV/AIDS landscape in Mexico and its idiosyncrasies. Presenting this extensive material in this chapter will facilitate the subsequent sections by avoiding re-introduction of concepts and terminology, and by providing the necessary context for succinct discussions and conclusions.

Overview of Molecular Biology and Pathogenesis of HIV/AIDS

The Acquired Immunodeficiency Syndrome (AIDS) is the disease caused by infection with the Human Immunodeficiency Virus (HIV). AIDS is characterized by marked suppression of the immune system, and such immunosuppression is associated with opportunistic infections, malignant tumors, wasting, and central nervous system degeneration. HIV infects various cells of the immune system, including macrophages and dendritic cells, but in particular it attacks CD4+ helper T lymphocytes. HIV evolved as a human pathogen fairly recently – as compared to most other human pathogens -, and the HIV epidemic was only identified during the 1980s[1].

The enormous medical and social burden of AIDS has led to an explosion of research aimed at deciphering HIV and its ability to sidestep and destroy host defenses. Academic literature on AIDS is vast and expanding. The following is a brief summary of HIV's molecular biology, epidemiology, pathogenesis and clinical features.

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[1] Abbas A. K., Lichtman A. H., Pillai S. (2007). *Cellular and Molecular Immunology* (6th ed., pp. 476-487). Philadelphia, PA: Saunders

HIV is a member of the lentivirus family of animal retroviruses. Lentiviruses are capable of short-term cytopathic effects and long-term latent infection of cells, and they produce slowly progressive, fatal diseases. Structurally, an HIV particle consists of two identical RNA strands packaged within a viral protein core and enveloped in a phospholipid bilayer derived from both virally encoded membrane proteins and host cell membrane **(see Figure 2-1)**. The RNA genome of HIV is approximately 9.2kb long and has the basic arrangement of nucleic acid sequences typical of all known retroviruses[2].

Figure 2-1: Structure of HIV[3]
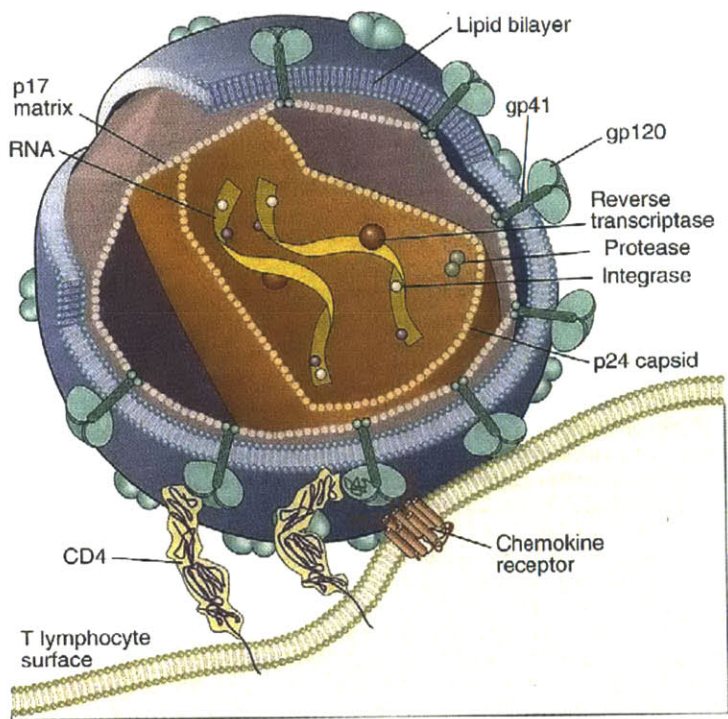
The viral particles that initiate infection are in the blood, semen, or other body fluids of an individual, and are transmitted to another individual via needle stick, sexual contact, or transplacental passage. HIV cell infection starts when envelope glycoproteins of the viral particle bind to both a CD4 receptor and a coreceptor (primarily CXCR4 and CCR5) that is a

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[2] Abbas A. K., Lichtman A. H., Pillai S. (2007). *Cellular and Molecular Immunology* (6th ed., pp. 476-487). Philadelphia, PA: Saunders
[3] *Ibid.*

member of the chemokine receptor family (**see Figure 2-1**). Upon viral binding, the CD4 and coreceptor induce a viral conformational change that enables the viral membrane to fuse with the target cell membrane.

All HIV strains can infect and replicate in CD4+ T cells that are activated in vitro. Some strains will infect macrophages but not continuous T cell lines (macrophage-tropic virus), while other strains will infect T cell lines but not macrophages (T-tropic virus). Some strains infect both T cell lines and macrophages (dual-tropic virus).

Once the HIV virion enters a cell, the enzymes within the nucleoprotein complex become active and begin the reproductive cycle. The nucleoprotein core is disrupted, the RNA genome is transcribed into a double-stranded DNA by viral *reverse transcriptase*, and the viral DNA enters the cell nucleus. Viral *integrase* catalyzes the integration of viral DNA into the host cell genome. The name provirus is given to the integrated HIV DNA. Current anti-retroviral therapies for HIV/AIDS include inhibitors of enzymes *integrase* and *reverse transcriptase*. The provirus may remain untranscribed for months or years, without production of new viral proteins or virions. Hence, HIV infection of an individual cell can be latent (**see Figure 2-2**).

Figure 2-2: HIV Life Cycle[4]
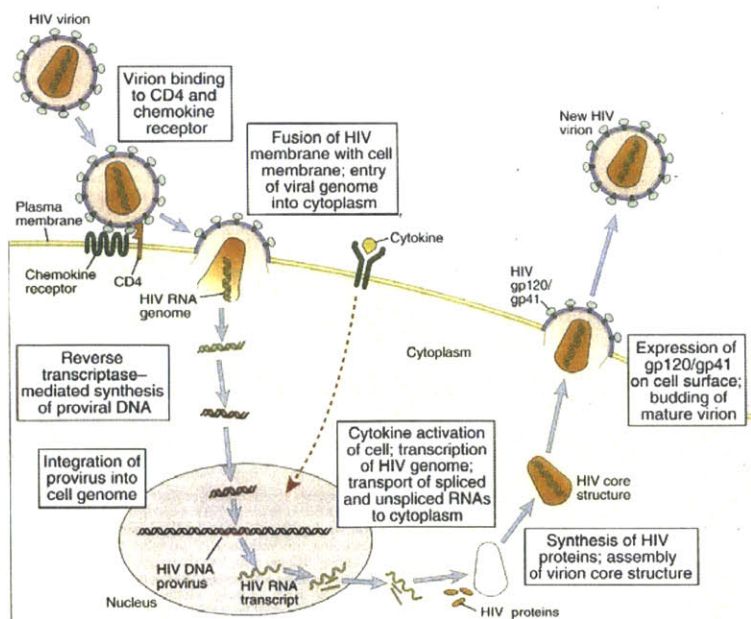
[4] Abbas A. K., Lichtman A. H., Pillai S. (2007). *Cellular and Molecular Immunology* (6th ed., pp. 479). Philadelphia, PA: Saunders

Initiation of the HIV DNA provirus transcription is closely linked to activation of the T cells by antigens or cytokines. This observation is significant to the pathogenesis of AIDS because the normal response of a latently infected cell to a microbe is likely the trigger for ending latency and initiating virus production.

The synthesis of mature, infectious viral particles begins after viral RNA transcripts are produced and the viral genes are expressed as proteins. The mRNAs that encode the various HIV proteins are derived from a single full-genome-length transcript by differential splicing events. After transcription of viral genes, viral proteins are synthesized in the cytoplasm. Infectious viral particles are assembled, and full-length RNA transcripts of the proviral genome are packaged within a nucleoprotein complex. This complex is then enclosed in a membrane envelope and released from the cell by budding from the plasma membrane.

Free viral particles released from one infected cell then bind to an uninfected cell, thus propagating the infection. Additionally, glycoproteins 41 and 120, which are expressed on plasma membrane of infected cells, can mediate cell-cell fusion with a CD4+coreceptor expressing uninfected cell, and HIV genomes can then pass between the fused cells directly.

The course of the disease begins with acute infection, which is partly controlled by the adaptive immune response, and then advances to chronic progressive infection of peripheral lymphoid tissues. Early (acute) infection is characterized by infection of memory CD4+ T cells in mucosal lymphoid tissues, and death of many infected cells. This local loss is reflected in considerable depletion of lymphocytes; in fact, within a couple of weeks, the majority of CD4+ T cells may be destroyed.

The transition from acute to chronic phase of infection is characterized by dissemination of the virus, viremia, and the development of host immune responses. Dendritic cells in epithelia capture the virus and migrate into the lymph nodes, then passing HIV on to CD4+ T cells. Viral replication at the lymph nodes leads to viremia. Meanwhile, the adaptive immune system mounts humural and cell-mediated immune responses, partially controlling infection and viral production. Such partial control is reflected by a drop in viremia within 10-12 weeks.

In the chronic phase of the disease, lymph nodes and the spleen are sites of continuous HIV replication and cell destruction. During this initial chronic phase, the immune system is

competent at handling most opportunistic infections, and few or no clinical manifestations of the HIV infection are present. This is the clinical latency period. However, destruction of CD4+ T cells within the lymphoid tissues steadily progresses, and the number of circulating blood CD4+ T cells steadily declines. Early in the course of the disease, the body may continue to make new CD4+ T cells, and therefore CD4+ T cells can be replaced almost as quickly as they are destroyed. Eventually, over the years, these cycles of virus infection, T cell death, and new infection leads to steady depletion of CD4+ T cells in the lymphoid tissues and in circulation (**see Figure 2-3**).

Figure 2-3: Progression of HIV Infection[5]

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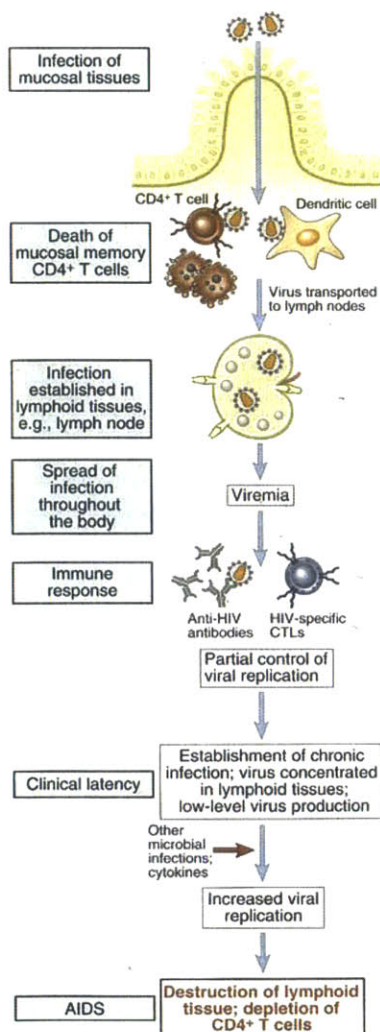
[5] Abbas A. K., Lichtman A. H., Pillai S. (2007). *Cellular and Molecular Immunology* (6th ed., pp. 481). Philadelphia, PA: Saunders

Immunodeficiency is created by both direct cytopathic effects of the virus and indirect effects. Most of the CD4+ T cell depletion is due to direct cytopathic effects of infection. For instance, the process of viral production and its budding with the cell membrane may lead to increased plasma membrane permeability and influx of lethal amounts of calcium, leading to apoptosis. Also, viral production interferes with cellular protein synthesis leading to cell death. Other, indirect mechanisms in addition to direct cell lysis/death have been proposed, including chronic activation of T cells that predisposes cells to apoptosis, and antibody-dependent cell-mediated cytotoxicity (ADCC) triggered after antibodies against HIV envelope proteins bind to HIV-infected CD4+ T cells.

HIV is transmitted from one individual to another by three main mechanisms: sexual contact, vertical transmission from mother to child, and inoculation of a recipient with infected blood or blood products. Sexual transmission is clearly the predominant mode of infection, constituting over 75% of all cases of HIV transmission[6]. In the US and the EU, major groups at risk of developing AIDS include men who have sex with men, intravenous drug abusers, heterosexual partners of members of other risk groups (e.g. female sex partners of male intravenous drug abusers), and children born of infected mothers. Conversely, heterosexual transmission is the dominant mode of HIV infection in Asia and Africa. Transmission of HIV by transfusion of blood or blood products has been nearly eliminated all around the world[7].

After viral entry, the clinical manifestations of the infection are divided in three phases: acute retroviral syndrome, chronic phase, in which most individuals are asymptomatic; and clinical AIDS. The acute retroviral syndrome is associated with an acute illness with nonspecific symptoms, including sore throat, myalgias, fever, weight loss, and fatigue. Other clinical features, such as rash, cervical adenopathy, diarrhea, and vomiting, may also occur. The viral load at the end of the acute phase reflects the equilibrium reached between the virus and the host response, and in a given patient it may remain fairly stable for several years. During this chronic phase of infection, patients are either asymptomatic or develop minor opportunistic

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[6] Kumar V., Abbas A. K., Fausto N., Aster J. (2010). Chapter 6: Diseases of the Immune System – Secondary Immunodeficiencies, *Robbins and Cotran Pathologic Basis of Disease* (8th ed). Philadelphia, PA: Saunders
[7] *Ibid.*

infections, such as oral candidiasis, vaginal candidiasis, herpes zoster, and even mycobacterial tuberculosis.

Because the loss of immune ability is directly linked to declining CD4+ T-cell counts, the Centers for Disease Control (CDC) classification of HIV infection separates patients into three categories: CD4+ cells greater than or equal to 500 cells/µL, 200 to 499 cells/µL, and fewer than 200 cells/µL. Clinically, blood CD4+ T-cell counts are the most reliable indicator of disease progression. *For this reason, CD4+ cell counts, and not viral load, are the primary clinical measurements used to determine when to start combination antiretroviral therapy*[8].

Clinical AIDS is characterized by the breakdown of host defenses, a dramatic increase in plasma virus, and severe clinical disease. Typically the patient presents with long-lasting fever, fatigue, weight loss, and diarrhea. After a variable period, serious opportunistic infections, secondary neoplasms, or clinical neurologic disease emerge.

Opportunistic infections constitute most deaths in untreated patients with AIDS. Approximately 15%-30% of untreated HIV patients develop pneumonia[9]. Many patients present with other opportunistic infections, involving pathogens such as Candida, cytomegalovirus, mycobacteria, Cryptococcus neoformans, Toxoplasma gondii, Cryptosporidium, herpes simplex virus, papovaviruses, and Histoplasma capsulatum. Furthermore, patients with AIDS have a high incidence of tumors, especially Kaposi sarcoma (KS), non-Hodgkin B-cell lymphoma, cervical cancer in women, and anal cancer in men. Between 25% and 40% of untreated HIV patients will develop a malignancy. Finally, involvement of the central nervous system is also a common manifestation of AIDS. Ninety percent of patients demonstrate some form of neurologic involvement at autopsy, and 40% to 60% have clinical neurologic dysfunction[10].

In the absence of treatment, most patients with HIV infection progress to AIDS after a chronic phase lasting from 7 to 10 years. Exceptions to this typical course include so-called rapid progressors, long-term nonprogressors, and elite controllers. In rapid progressors the chronic phase lasts only 2 to 3 years after primary infection. About 5% to 15% of infected

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[8] Kumar V., Abbas A. K., Fausto N., Aster J. (2010). Chapter 6: Diseases of the Immune System – Secondary Immunodeficiencies, *Robbins and Cotran Pathologic Basis of Disease* (8th ed). Philadelphia, PA: Saunders
[9] *Ibid.*
[10] *Ibid.*

individuals are long-term nonprogressors, who remain asymptomatic for 10 years or more, with stable CD4+ T-cell counts and low levels of plasma viremia. Elite controllers are the remarkable 1% of infected individuals who have undetectable plasma virus[11]. This latter elite controllers group has been the target of great academic and research attention, as their extraordinary ability to elude infection progression might hold some clues to unlocking vaccines or cures for HIV/AIDS.

The Disruptive Theory of Innovation

Disruptive innovation, a term coined by Clayton Christensen, describes the process by which a product or service takes root initially in simple applications at the *bottom* of a market and then moves *up market*, eventually displacing established competitors[12].

Innovations that are disruptive allow either new populations of consumers to access a product or service that was historically inaccessible economically or due to skill level, or a given population to access simpler or more economical versions of an existing product or service.

The disruptive theory of innovation is rooted in the premise that most companies innovate faster than their customers' lives change, hence addressing the needs of their most sophisticated and demanding customers. Therefore, *incumbent* companies pursue *sustaining innovations* that perpetuate this trend, offering products and services that improve and sophisticate over current offerings. Given this dynamic, a specific customer segment is bound to evolve, wherein the current offerings are "overshooting" their needs. These customers are said to be *overserved* by the incumbent company. Simpler, less sophisticated, cheaper or more accessible versions of the product or service (i.e. disruptive innovations) may very well address their needs. As a consequence, companies that pursue sustaining innovations usually open doors to innovations that are disruptive, innovations which may eventually move up market and displace established competitors **(see Figure 2-4)**.

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[11] Kumar V., Abbas A. K., Fausto N., Aster J. (2010). Chapter 6: Diseases of the Immune System – Secondary Immunodeficiencies, *Robbins and Cotran Pathologic Basis of Disease* (8th ed). Philadelphia, PA: Saunders
[12] Christensen C. M. (2012). Key Concepts – Disruptive Innovation. Retrieved from http://www.claytonchristensen.com/disruptive_innovation.html

Figure 2-4: Disruptive Innovations versus Sustaining Innovations[13]
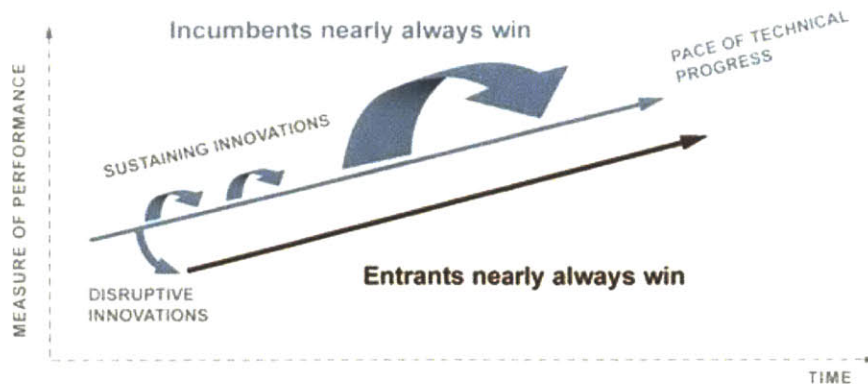
The theory is also rooted in the observation that *disruptors* (i.e. companies following disruptive models of innovation) have a higher likelihood of both surviving and succeeding, mainly because i) they are not serving the same customer segment as the incumbent, and ii) either margins or per unit revenues are typically much lower than in the incumbent's line of business.

Christensen distinguishes between *low-end disruption* which targets customers who do not need the full performance valued by customers at the high end of the market, and *new-market disruption* which targets customers who have needs that were previously ignored or unserved by existing incumbents[14].

In *The Innovator's Solution,* Christensen explores several cases of disruptive innovations, from the disk drive industry, and the excavating equipment industry (hydraulic actuation slowly displacing cable-actuated movement), to interventional cardiology and angioplasty (low-end disruption to CABG surgery).

Disruptive innovations do not discriminate among industries, and the healthcare industry has also seen a handful of business models with the characteristics of disruptive models of innovation. One example is the retail medical clinic: models like *CVS' Minute Clinic* and *Walgreen's Take Care Clinic* in the US, and *Farmacias Similares* in Mexico, exhibit some of

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[13] Christensen C. M. (2012). Key Concepts – Disruptive Innovation. Retrieved from http://www.claytonchristensen.com/disruptive_innovation.html
[14] Christensen C. M., Raynor M. E. (2003). *The Innovator's Solution. Creating and Sustaining Successful Growth* (1st ed., pp. 31-72). Boston, MA: Harvard Business School Press

the characteristics of a low-end disruption, and seem to be displacing services that were traditionally covered by the primary care physicians' office. By offering care for a limited number of basic conditions, and doing so i) at relatively low costs, ii) with short waiting times, and iii) in convenient locations and schedules, they are serving patients with basic medical needs that would have otherwise been overserved by the primary care physician's office. Retail medicine is still in its early stages, yet this model has opened the door for disruptive innovations to enter the health delivery space. The fact that the number of US retail medicine clinics has risen from less than 200 in 2006 to more than 1,100 in 2009[15], and that the number of visits to retail clinics grew at ~100% CAGR from 2007 to 2009[16], is evidence to support the disruptive role retail clinics are having in the healthcare industry.

The diagnostics industry is another one where disruptive models may have a significant impact. Most diagnostics companies focus on high-cost, high-performance diagnostics (performance commonly indicated by high specificity and sensitivity). Physicians, as well, commonly favor the higher sensitivity and specificity diagnostics, as they facilitate their medical decision making. However, low-end disruptive models of innovation have started to evolve. The tradeoff of lower performance (lower specificity and sensitivity) is now made in exchange for the less complex, more accessible, faster, or/and less expensive diagnostic alternatives. It appears, therefore, that new groups of overserved customers/patients may be more conveniently served via models of disruptive innovation.

Among the emerging group of disruptive diagnostic models, the *Point-of-Care (POC)* diagnostic concept, in which the diagnosis is taken from centralized laboratory facilities and brought to unsophisticated patient environments such as local town health centers, has become a focus of both attention and efforts in academia, public health, and industry sectors. It is this particular healthcare phenomenon of *Point-of-Care* diagnostics, and the impact that it may have in the management of HIV/AIDS, that is at the core of this thesis discussion.

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[15] Keckley P. H., Underwood H. R., Gandhi M. (2009). Retail Clinics: Update and Implications. *Disruptive Innovations in Healthcare, article 8, Deloitte Center for Health Solutions*
[16] Mehrotra A., Lave J. R. (2012). Visits to retail clinics grew fourfold from 2007 to 2009, although their share of overall outpatient visits remains low. *Health Affairs, 31 (No 9)*, pp. 1-7

Point-of-Care Diagnostics in HIV/AIDS

In the developing world, most diagnostic laboratory tests are done away from the point of contact with the patient; they are usually performed in centralized laboratories, typically in large urban settings. For patients outside these urban settings there are logistical barriers of transporting samples from the point of care to the centralized laboratory, as well as the expected delays in intervention or loss of follow-up care. The reasons why the centralized model of laboratory diagnosis is the most widespread are straightforward: laboratory equipment requires significant capital investment, as well as skilled science and health professionals to operate the equipment, making a centralized model the more feasible option for resource-constrained settings.

Consequently, poor and/or rural populations in low and middle-income countries have limited access to diagnostic laboratories. The past decade has seen technological advancements, increased investment, and greater awareness about the importance of *Point-of-Care* (POC) diagnostics. Providing fast, affordable, portable, and reliable POC tests, requiring little training and often times no electricity, is becoming a priority among healthcare officials and diagnostic company executives in low and middle-income countries[17].

Such interest in POC tests has also intensified in the management and treatment of HIV/AIDS in low-income countries, particularly for its use in CD4+ T lymphocyte counts[18]. As previously mentioned, the CD4+ cell count is the primary clinical measurement used to determine eligibility for antiretroviral therapy (ART) in patients diagnosed with HIV. CD4+ counts, along with viral load measurements, also monitor the efficacy of ART after being initiated. The importance of ART initiation, and hence of prompt and accurate CD4+ counts, stems from the fact that ART considerably decreases viremia and slows progression of HIV into AIDS[19]. Furthermore, if CD4+ counts are established, ART prophylaxis can significantly reduce

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[17] Peeling R. W., Mabey D. (2010). Point-of-care tests for diagnosing infections in the developing world. *Clinical Microbiology and Infectious Diseases, CMI, 16,* pp. 1062-1069

[18] Zachariah R., Reid S. D., Chaillet P., Massaquoi M., Schouten E. J., Harries A. D. (2011). Why do we need a point-of-care CD4 test for low-income countries? *Tropical Medicine and International Health, 16 (No I),* pp. 37-41

[19] Sterne J. A. *et al.* (2009). Timing of initiation of antiretroviral therapy in AIDS-free HIV-1 infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet, 373,* pp 1352-1363

the risk of mother to child transmission of HIV during pregnancy, childbirth and breastfeeding[20], as well as notably reduce the rates of sexual transmission of HIV in serodiscordant couples (i.e. where one member is infected and the other is not)[21].

Access to POC tests at the site of patient care could significantly improve management and treatment of HIV/AIDS in suburban and rural areas, by i) more easily assessing eligibility for ART, ii) initiating ART more promptly, iii) improving prevention of mother to child transmission, iv) reducing early attrition, and v) enhancing ART progress and control. Although reliable, fast, affordable and portable POC CD4+ tests are not yet widely available, several CD4+ count products are currently in development or marketed, which might change the standard of how CD4+ counting is performed in low and middle-income countries.

Before describing these innovative products, I believe it is important to provide a brief overview of the available technologies for CD4+ counting, including the gold standard flow cytometry, manual CD4+ count methods, the diverse kinds of automated imaging cytometry, microflow cytometry, and electrical and mechanical sensing. Following this technology review, a summary of the more promising commercial, or near-commercial, CD4+ tests available is presented.

The flow cytometry method, the gold standard of cell counting, uses antibodies to human CD4+ for cell capture and for fluorescently labeling antibody conjugates, and combines them with optics for cell sorting and counting. Fluorescence-activated cell sorting (FACS) by flow cytometry is the primary CD4+ cell counting methodology in the world. The two devices with the highest share worldwide are Becton Dickinson's FACSCalibur and Beckman Coulter's EPICS XL/MCL[22].

Dual flow cytometry uses a hematological analyzer in addition to a flow cytometer, to assess absolute CD4+ count and the fraction of CD4+ to the entire leukocyte population, while single flow platforms use only flow cytometer for absolute CD4+ count in a fixed volume (e.g.

[20] WHO (2010). *Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a Public Health Approach,* World Health Organization
[21] Cohen M. S. *et al.* (2011). Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *The New England Journal of Medicine, 365 (No 6),* pp. 493-505
[22] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1),* pp. 45-54

Merck's Guava EasyCD4, Partec's CyFlow CD4, PointCare Technologies' PointCare Now, and Becton Dickinson's FACScan and FACSCount). Single platform technologies are less costly and easier to operate, and are becoming the equipment of choice in smaller, albeit still centralized, laboratory facilities[23].

Flow cytometry, however, is limited to central laboratory use, implying that samples collected in rural and sub-urban areas must be shipped in order to obtain results. Even more so, the need for shipping puts the samples at risk, while at the same time requiring longer than ideal waiting times for results.

Manual counting methods, however, can be performed at the point of care. These manual tests require a powerful microscope (at least 40x objective), a hemocytometer, calibrated pipettes, test tubes, refrigeration of reagents, and a manual counter. While this method correlates closely with flow cytometry measurement, sample preparation and manual counting is laborious, and it requires training programs and strict quality controls, making it a sub-optimal and difficult to scale option[24].

In an effort to develop technology that may be used in decentralized settings, extensive development in microfluidic technologies and counting devices has been conducted. Given the microfluidic nature of technology, only small samples of blood are required for analysis, thus eliminating the need for venous blood draw, and therefore drastically simplifying the sample collection step in CD4+ count measurements. Furthermore, microfluidics-based technologies greatly reduce amount of reagents and liquid waste, making it feasible to assemble an entire test in a single disposable cartridge.

In a typical imaging cytometer, an optical detector images a surface on which fluorescently stained CD4+ cells are captured. The blood sample is first mixed with antibodies conjugated to magnetic beads, with each type of antibody labeled with a different fluorescent tag. The mixture is then injected into a microchannel in which different types of cells are separated with the aid of the magnetic beads, to finally result in CD4+ and CD8+ cells being

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[23] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1)*, pp. 45-54
[24] *Ibid.*

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[23] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1)*, pp. 45-54
[24] *Ibid.*

excited by LEDs[25]. Imaging cytometry is a single platform approach, obtaining absolute CD4+ counts and not the ratio to total leukocytes. A recent study showed similar performance to flow cytometry in an HIV infected cohort of 460[26], making it in principle a viable technology for POC settings. Nonetheless, blood dilution and staining are yet to be standardized and automated.

To overcome the complex optics involved in fluorescence imaging, chemiluminescence has also been used for CD4+ counts. Cells are captured inside an immunoaffinity microchannel after which they are labeled with antibodies that are also conjugated with an enzyme that catalyzes the chemiluminescent reaction detected by a photoreceptor. This form of photodetection was found to be proportional to the number of captured cells[27].

Imaging cytometry, in general, has several distinct advantages over FACS when it comes to POC setting. Being a single platform of smaller scale it is a potentially portable technology. Furthermore, imaging cytometry detects multiple cells simultaneously, whereas FACS measures one cell at a time, making imaging cytometry a faster, and simpler, alternative.

Efforts have also been made in developing micro-sized, low-cost flow cytometers, or microflow cytometers, for the purpose of CD4+ counting. Various methods have been investigated and some developed, including mechanical structures, optical forces, dielectrophoresis, hydrodynamic forces, ultrasound effects, and electrokinetic transport. Based on these principles, several compact flow cytometer prototypes that are handheld, battery powered, and low cost, have been constructed. Preliminary evaluations of these prototypes for CD4+ counting resulted in similar performance to FACS[28].

Moreover, electrical and mechanical sensing systems allow for the development of more portable, simpler and rugged devices. Since they do not rely on lenses and focusing for

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[25] Lumb R., et al. (2006). Not all microscopes are equal. The International Journal of Tuberculosis and Lung Disease, 10, pp. 227–229

[26] Li, X., et al. (2010). Clinical evaluation of a simple image cytometer for CD4 enumeration on HIV-infected patients. Cytometry Part B – Clinical Cytometry, 78, pp. 31-36

[27] Wang, Z., et al. (2010). Microfluidic CD4+ T-cell counting device using chemiluminescence-based detection. Analytical Chemistry, 82, pp. 36-40

[28] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. Trends in Biotechnology, 30 (No 1), pp. 45-54

analysis, the size and complexity of these types of devices are greatly diminished. Another set of preliminary tests showed excellent correlation with optical measurements[29].

Taking the previously described technological advances in cell counting, a small number of devices have been recently developed (some of which are already commercially available), which promise to be the pioneers in disruptive, point-of-care CD4+ counts. Most of them use fingerstick blood samples, are robust, fast, have flexible power options, and use stable reagents enclosed in a cartridge.

The PointCare NOW (Point Care) and the CyFlow miniPOC (Partec) are modified flow cytometers. Although less expensive and smaller that standard flow cytometers, they are still not portable, and require vein puncture for blood sample collection, therefore substantially limiting their POC potential.

Alternatively, Pima CD4 (Alere) is the first commercially available CD4+ count test that does not use traditional flow cytometry. The Pima uses fluorescence image analysis, resulting in absolute CD4+ count per ml. Standardized cartridges are intended for daily quality control testing[30]. Evaluations conducted in sub-Saharan Africa showed good performance when compared to standard flow cytometry[31].

Daktari Diagnostics is also in the final developing stages of its Daktari CD4. This device uses microfluidic affinity-chromatography and shear-gradient techniques to capture CD4+ cells, and employs non-optical detection to count them. The test is composed of a reader device and a disposable cassette that contains all of the reagents. The CD4+ cells adhere to an antibody coated chamber, other cells are subject to large shear forces and do not bind. The bound CD4+ cells are then lysed and the release of ions is measured by impedance spectroscopy[32]. The cartridge with the blood sample is placed in the instrument. Reagents then are released from the blister pack and pass into the test chamber. The blood moves at a predefined flow rate through a chamber functionalized with monoclonal antibodies, resulting in shear-gradient

[29] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1)*, pp. 45-54

[30] *Ibid.*

[31] Jani I.V., *et al.* (2011). Accurate CD4 T-cell enumeration and antiretroviral drug toxicity monitoring in primary healthcare clinics using point-of-care testing. *AIDS, 25 (No 6)*, pp. 807-812

[32] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). *op. cit.*

enhanced chromatographic separation. The retained CD4 cells are lysed and the released ions are detected by impedance spectroscopy, the signal of which correlates to the CD4 count **(see Figure 2-5)**.

Figure 2-5: Working Principles of the Daktari CD4 Count Analyzer[33]
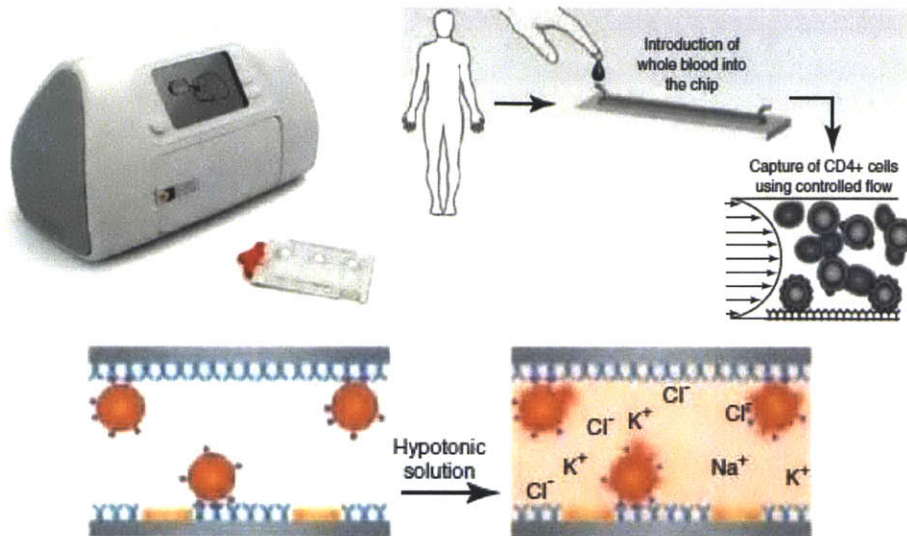
The decrease in impedance has been shown to correlate with cell count over three orders of magnitude[34]. Preliminary measurements in a HIV infected cohort of 49 demonstrated sensitivities for distinguishing clinically relevant thresholds of 200, 350 and 500 cells/uL of 0.86, 0.90 and 0.97, respectively. Specificity was shown to be 0.94 or higher at all thresholds[35].

It is important to emphasize that the Daktari CD4 count is the device around which the primary thesis hypotheses will be centered. While extrapolations and generalizations are made in the field of POC diagnostics, direct interpretations of clinical needs and market size estimations will be conducted based on the characteristics of Daktari CD4 as the platform POC technology. This should not be interpreted, however, as a suggestion that the calculated

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[33] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1)*, pp. 45-54

[34] Cheng X., *et al.* (2007). Cell detection and counting through cell lysate impedance spectroscopy in microfluidic devices. *Lab on a Chip, 7*, pp. 746-755

[35] Cheng X., *et al.* (2007). A microchip approach for practical label-free CD4+ T-cell counting of HIV-infected subjects in resource-poor settings. *Journal of Acquired Immune Deficiency Syndromes (JAIDS), 45*, pp. 257-261

economic potential for POC CD4 count diagnostics in Mexico corresponds exclusively to Daktari, as there are current and future competitors that will battle for a presence in this POC market.

Finally, mBio Diagnostics' SnapCount is another CD4+ cell count system in development. This particular analyzer is a static two-color fluorescence imaging cytometry system, which uses disposable cartridges and a simple reader with immunostaining of blood samples. This device addresses the high complexity and cost typical of optical instruments by using LightDeck technology, a fluorescence illumination method that uses low-cost lasers, optics and imaging sensors that are now common in most cell phones. The primary advantage of SnapCount is its relatively high throughput (10 samples/h)[36].

Figure 2-6 provides pictures of both Alere's Pima device and mBio's SnapCount, paired with their respective working principle schematic representations. **Figure 2-7** provides additional, detailed specifications of existing POC CD4 tests, including but not limited to those of Alere, Daktari and mBio:

Figure 2-6: Working Principles of Alere's Pima and mBio's SnapCount CD4 Count Devices[37]
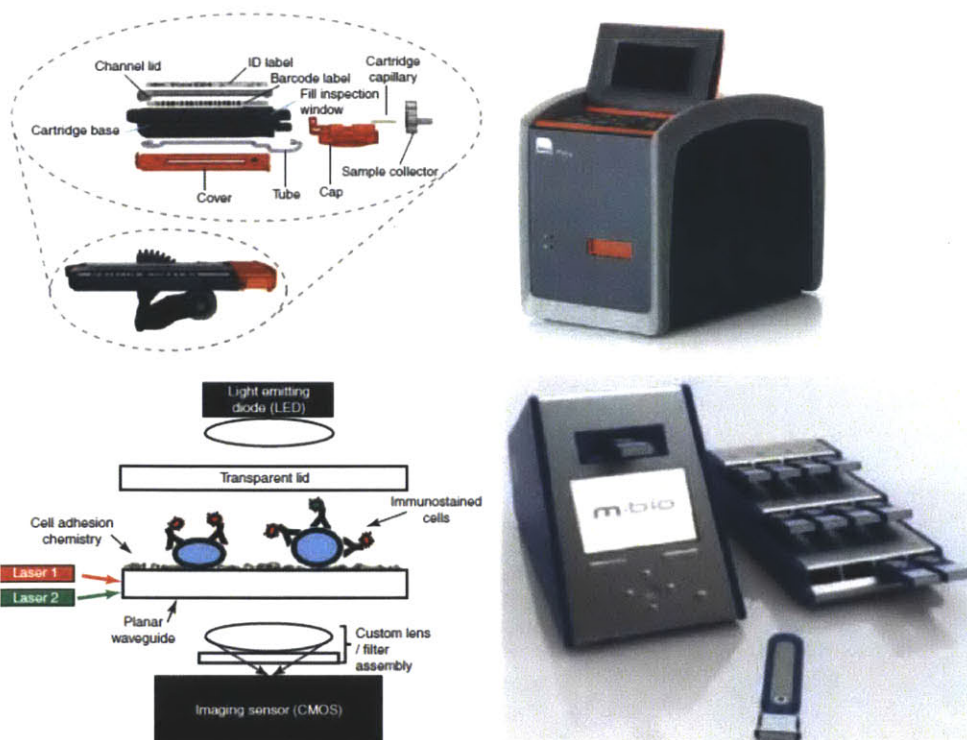
[36] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1)*, pp. 45-54
[37] *Ibid.*

Figure 2-7: Specifications of Existing POC CD4 Test Technologies[38]

Instrument	Sample volume (μl)	Stabilized reagents	CD4/CD4%	Time to result (min)	Instrument required	Automation/throughput h⁻¹	Data storage	Battery run time per charge (h)	Marketed	QC	Regulatory status	Dimensions L×W×H (cm)[a]	Weight (kg)	Manufacturer website
PointCare NOW™	40	Y	Y/Y[b]	8	Y	Y/5–6	Y	Y/4	Y	Y	FDA/CE	33.7×25.0×35.4	<12	http://www.pointcare.net/
CyFlow® miniPOC	20	Y	Y/Y	1	Y	Y/30–40	Y	Y/4–5	Y	Y	CE	18.6×26.8× 24.3	<5	http://www.partec.com/
Pima™	25	Y	Y/N	20	Y	Y/3	Y	Y/8	Y	Y	CE	22×13×16, 9.7×3.2×0.6	2.54,0.11	http://www.alere.com/
Coulter® CD4 Count Kit	100	N	Y/N	30	Y	N/2[c]	N	N	Y	Y	CE	NA	NA	http://www.beckmancoulter.com/
Dynal T4 Quant Kit	125	N	Y/N	30	Y	N/6[c]	N	N	Y	NA	CE	NA	NA	http://www.invitrogen.com/
Daktari	10	Y	Y/N	8	Y	Y/7	Y	Y/NA	N	NA	NA	22.9×12.7×17.8, 0.80×5.65×1.08	2.5, 0.03	http://www.daktaridx.com/
mBio	10	Y	Y/N	20	Y	SA/8–10	Y	Y/NA	N	NA	NA	38×19×15, 0.88×0.30×0.13	3, 0.016	http://www.mbiodx.com/

[a]Instrument dimensions precede cassette dimensions where listed.
[b]This is the CD4% versus total lymphocyte reading.
[c]To minimize reader error, a limit of eight specimens per day should be read.

Among these devices, there is no particular one that is widely used, or that has yet developed a strong commercial presence, except perhaps for Alere's Pima since it was the first one to be approved and marketed among the three (Pima, Daktari, and SnapCount). All three devices gather the basic characteristics of POC settings, such as size, relative portability, specimen volume, reagent stability, simple user interface, and comparable sensitivity and specificity.

One area of difference is quality control. While Pima incorporates QC indicators, the devices being developed by Daktari and mBio offer cartridge-based instrument readers with single or no moving parts. This simplified instrumentation may very well lower failure rates as well as diminish the need for frequent QC or maintenance.

The Mexican Healthcare System

Mexico's demographic development (population of ~107 million in 2008) has been characterized by a decrease in mortality (from 27 deaths per 1000 in 1930 to 4.9 in 2008), an increase in life expectancy (from 34 years in the 1930s to 75 in 2008), and a sharp decrease in fertility rates (from 7 births per woman in reproductive age in the 1970s to 2.1 in 2008)[39].

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[38] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1),* pp. 45-54
[39] Consejo Nacional de Población. Indicadores Demográficos Básicos (2012). Retrieved from http://www.conapo.gob.mx/es/CONAPO/Indicadores_demograficos_basicos

These three phenomena have resulted in an aging population, with a growing proportion of senior citizens. The marked increase in life expectancy, added to the rising exposure to so-called emerging risks (mainly due to unhealthy lifestyles), have modified the main causes of death in the country. The epidemiologic transition into noncommunicable diseases (NCDs) and lesions as the main causes of death is self-evident. 60 years ago, roughly 50% of all deaths were due to common infections, reproductive illnesses, and malnutrition. Today, these diseases represent less than 15% of all deaths, while NCDs and lesions represent 75% and 11%, respectively. Diabetes alone, as the principal cause of death, claims 17% of deaths in women, and 12% of the deaths in men[40] (**see Figure 2-8**).

Figure 2-8: Main Causes of Death in Men and Women in Mexico[41]

Top 10 Causes of Death in Men, Mexico, 2008

	Number	Rate (per 100,000)	%
1. Diabetes	35,697	68.04	11.87%
2. Ischemic heart diseases	33,804	64.43	11.24
3. Cirrhosis and other chronic liver diseases	21,464	40.91	7.13
4. Cerebrovascular diseases	14,388	27.42	4.78
5. Homicides	12,575	23.97	4.18
6. Chronic obstructive pulmonary diseases (COPD)	11,590	22.09	3.85
7. Motor vehicle accidents	9,643	18.38	3.21
8. Acute lower respiratory infections	8,088	15.42	2.69
9. Hipertensive diseases	6,806	12.97	2.26
10. Nephritis and nephrosis	6,786	12.93	2.26
Poorly defined causes	5,319	10.14	1.77
All other diseases	134,677	256.69	44.77
Total	**300,837**	**573.39**	**100**

Top 10 Causes of Death in Women, Mexico, 2008

	Number	Rate (per 100,000)	%
1. Diabetes	39,939	73.67	16.74%
2. Ischemic heart diseases	25,994	47.95	10.90
3. Cerebrovascular diseases	15,857	29.25	6.65
4. Chronic obstructive pulmonary diseases (COPD)	8,994	16.59	3.77
5. Hipertensive diseases	8,902	16.42	3.73
6. Acute lower respiratory infections	7,024	12.96	2.94
7. Cirrhosis and other chronic liver diseases	6,972	12.86	2.92
8. Nephritis and nephrosis	5,814	10.72	2.44
9. Breast cancer	4,835	8.92	2.03
10. Protein-calorie malnutrition	4,241	7.82	1.78
Poorly defined causes	5,185	9.56	2.17
All other diseases	104,766	193.24	43.92
Total	**238,523**	**439.95**	**100**

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[40] Gómez Dantés O., Sesma S., Becerril V. M., Knaul F. M., Arreola H., Frenk J. (2011). Sistema de Salud de México. *Salud Pública de México, 53, supl 2,* S220-S232
[41] *Ibid.*

The Mexican healthcare system is divided in two sectors: public and private. Within the public sector, there are the institutions of Social Security [*Instituto Mexicano del Seguro Social* (IMSS), *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado* (ISSSTE), *Petróleos Mexicanos* (PEMEX), *Secretaría de la Defensa* (SEDENA), *Secretaría de la Marina* (SEMAR), among others], and those institutions that care for populations without Social Security [*Secretaría de Salud* (SSa), *Servicios Estatales de Salud* (SESA), *Programa IMSS-Oportunidades* (IMSS-O), and *Seguro Popular de Salud* (SPS)]. The private sector includes private insurers and a variety of providers such as clinics, hospitals, and physician private practices.

The amount and quality of care received depends very much on the type of coverage that an individual qualifies for. Accordingly, the Mexican population can be divided in three groups: i) salaried workers, pensioned retirees and their families, ii) self-employed, informal sector workers, unemployed, out of labor force individuals, and their families, and iii) population with significant financial capabilities.

The first group, the "workers", benefits from the Social Security institutions, which cover ~48 million people. IMSS alone covers more than 80% of this group, with its own hospitals, physicians and nurses. ISSSTE, which is responsible for government employees, retirees and their families, covers another 18% of this group of "workers", also with its own resources. PEMEX and the other institutions cover the remaining[42].

The second group, the "uninsured", has traditionally sought healthcare through the SSa (Secretary of Health), the SESA (State Health Services) and IMSS-O on an assistance by availability basis. In 2003, however, the Mexican Congress approved the Health General Law Reform that gave birth to the *Sistema de Protección Social en Salud (SPSS)* and its operating entity the *Seguro Popular*. This new system, introduced and avidly supported by former Minister of Health (and current Dean of the Harvard School of Public Health) Dr. Julio Frenk, set itself the goal of covering the healthcare needs of those individuals excluded from the traditional Social Security (~57 million people). By 2009, the *Seguro Popular* had ~31 million affiliates under its umbrella. While coverage has increased dramatically in a short period of

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[42] Gómez Dantés O., Sesma S., Becerril V. M., Knaul F. M., Arreola H., Frenk J. (2011). Sistema de salud de México. *Salud Pública de México, 53, supl 2,* S220-S232

time, there are still ~26 million without health coverage. It is estimated that three fourths of these ~26 million are the responsibility of the SSa and the SESA, and the remaining fourth is the responsibility of the IMSS-O[43].

The third group, a minority with higher purchasing power, receives care almost exclusively through the private system of payers and providers **(see Figure 2-9).**

Figure 2-9: Structure of the Mexican Healthcare System
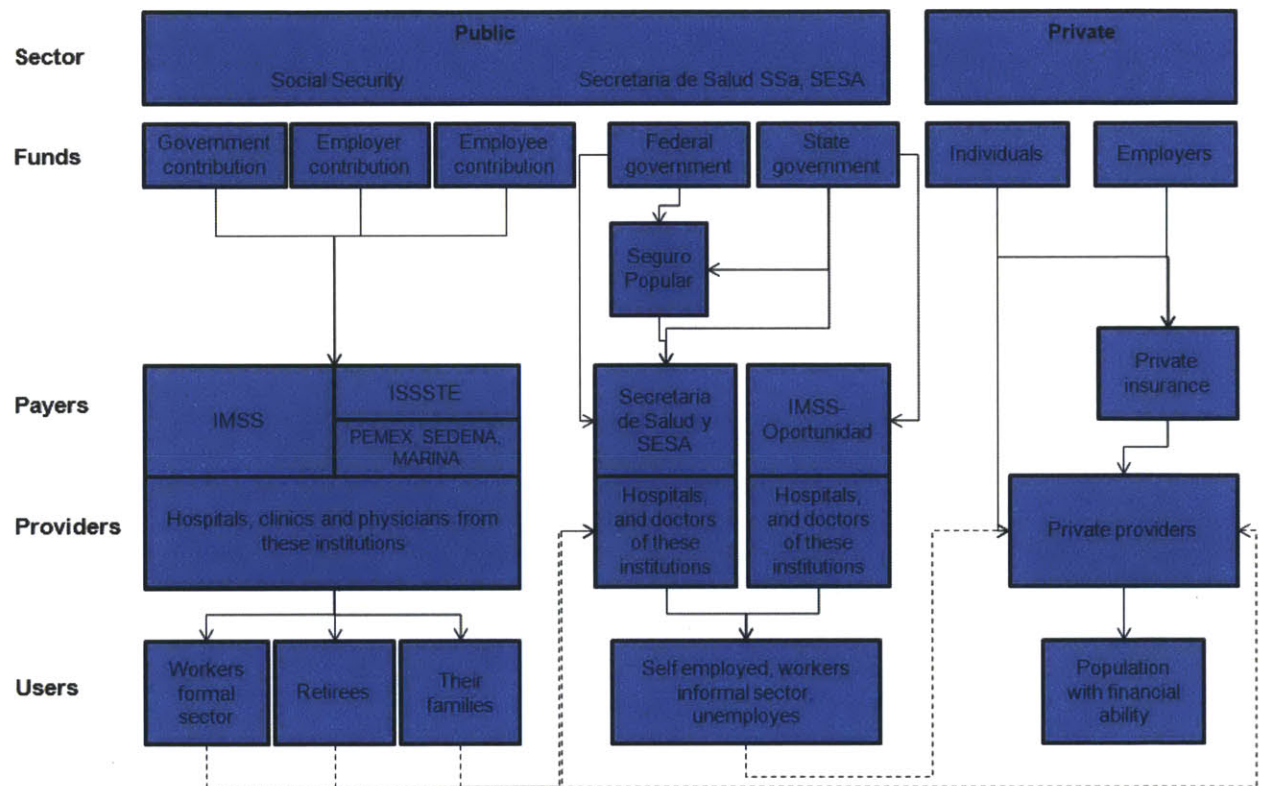
Financial contribution to the IMSS is mandatory for individuals in the "workers" group. IMSS guarantees medical, surgical, pharmaceutical, and hospital care, as well as maternity assistances and subsidies for temporary incapacities. The "uninsured" may contribute to IMSS on a voluntary basis, in order to gain similar sickness and maternity coverage. Those affiliated with the ISSSTE (i.e. state employees and retirees, and their families), and those in PEMEX,

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[43] Chertorivski-Woldenberg S. (2011). Seguro Popular: logros y perspectivas. *Gaceta Médica de México, 147,* 487-496

SEDENA and SEMAR (PEMEX employees, armed forces, etc.), receive medical benefits that are very similar to those of the IMSS.

Conversely, those "uninsured" individuals covered by Seguro Popular currently have access to care for 284 pre-defined interventions, including detection and preventive medicine, ambulatory medicine, dental health, reproductive and maternal health, rehabilitation, emergencies, hospitalizations and surgical care. These interventions are approved and defined through the Catálogo Universal de Servicios de Salud (CAUSES), which is updated on an annual basis. Additionally, there are 50 high-cost interventions, financed through the Fondo de Protección contra Gastos Catastróficos fund (FPGC), covering high-burden diseases and treatments, including pediatric, cervical and breast cancers; neonatal intensive care; and diagnosis and comprehensive treatment of HIV/AIDS[44]. All of these interventions and services, though financed by Seguro Popular, are managed by each state's Secretary of Health, and provided through each state's facilities of the SSa and SESA.

It should be mentioned that the funds assigned to states for high-cost interventions, the FPGC, have never been consumed in their entirety by any state in any given year since the fund's inception. This leads to two pertinent observations: i) there exists some financial flexibility for diagnostics, care, and treatments under this high-cost list, and ii) there is momentum for ambitiously expanding coverage into cardiovascular and cerebrovascular diseases, oncology, and transplants, among others.

The "uninsured" individuals, who are not covered by Seguro Popular, receive care through each state's SSa and SESA units, care that includes basic ambulatory care in most centers, and relatively more robust care in the major cities.

Finally, the IMSS-O offers basic health services, mainly in rural areas, through a network of rural hospitals. Care is focused on general ambulatory medicine, as well as on maternal and neonatal hospital services.

Health services through IMSS are financed by three contributions: one by the employer (which, in the case of ISSSTE, PEMEX, SEDENA and SEMAR, the employer is the government

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[44] Bernal F (2012). Sistema de Protección Social en Salud [PowerPoint slides], Seguro Popular

itself), one by the employee, and one by the government. IMSS-O is financed directly by the federal government, even though it is managed by the IMSS.

The *Seguro Popular* is financed primarily by the federal government (~75%), while each state contributes the remaining amount, thus constituting each state's *Seguro Popular* budget. Out of the assigned budget to each state, ~89% is destined for the care of *Seguro Popular* affiliates under the general CAUSES intervention catalog, ~8% is assigned to the FPGC and the high-cost interventions, and ~3% is spent on infrastructure investment and/or unanticipated demand (e.g. this last portion was crucial in treating the H1N1 epidemic)[45]. The *Seguro Popular* purchases the care for its affiliates to the SSa and the SESAs. Basic care expenses incurred by the SSa and the SESAs, corresponding to "uninsured" who are outside of *Seguro Popular* are also funded mainly by federal government, although a portion is matched by each state.

Primarily due to the creation of the *Seguro Popular,* the percentage of GDP spent on healthcare increased from 5.1% in 2000 to 5.9% in 2008, although it is still below the Latin American average (6.9%), and significantly lower than in other countries like Argentina (9.8%) or Colombia (7.4%). Most of this expenditure corresponded to the SSa (~45%), followed by IMSS (~42%) and the ISSSTE (~10%)[46]. The pharmaceutical expenditure represented 24% (2007) of the total health expenditure, or 1.4% of GDP. The availability of pharmaceuticals has improved over the years to an average of ~89% in stock when the drug was requested, particularly in the SSa and SESA ambulatory centers where *Seguro Popular* affiliates are attended[47].

It is important to note that hospital accreditation and evaluation is conducted by the *Consejo de Salubridad General.* This organization also plays a vital role in scientifically and medically accepting and recommending new devices, diagnostics and pharmaceuticals into the Mexican system. The sign-off by this council is a separate and necessary step in addition to the formal regulatory approval, which in conducted by the COFEPRIS, *Comisión Federal para la*

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[45] Bernal F (2012). *Sistema de Protección Social en Salud* [PowerPoint slides], Seguro Popular
[46] Gómez Dantés O., Sesma S., Becerril V. M., Knaul F. M., Arreola H., Frenk J. (2011). Sistema de salud de México. *Salud Pública de México, 53, supl 2,* S220-S232
[47] Chertorivski-Woldenberg S. (2011). Seguro Popular: logros y perspectivas. *Gaceta Médica de México, 147,* 487-496

Protección contra Riesgos Sanitarios The COFERPIS, as an agency, is part of the SSa but enjoys operating and technical autonomy for the fulfillment of its control and regulatory roles.

Overall, the Mexican healthcare system is in the process of expanding its coverage in an accelerated matter. The creation of the *Seguro Popular* is, without a doubt, the most aggressive initiative in Mexican healthcare over the past decades; this initiative promises to close the gap between the "workers" and the "uninsured" populations, while also expanding the coverage in the most isolated and marginal regions of the country.

The Landscape of HIV/AIDS in Mexico

The degree of morbidity and mortality caused by HIV, and the global impact of HIV infection on health care resources and economics are enormous and continue to grow. As of 2008, 31-36 million people lived with HIV worldwide, of which some ~2.7 million were infected in 2008 alone. HIV has caused the death of over 25 million adults and children. Of those currently living with HIV, approximately 68% are in sub-Saharan Africa. HIV/AIDS is particularly devastating, because roughly half of the new cases every year occur in young adults aged 15 to 24. Consequently, AIDS has left approximately 16 million orphans worldwide[48]. Currently there is no effective vaccine or cure for AIDS, however several anti-retroviral therapies have been developed, which, in many cases, have been successful in markedly slowing the progression of infection and the associated syndromes.

The epidemiologic picture is Latin America, while relevant, is not as stark as that of sub-Saharan Africa. In 2008, there were approximately 2.2 million people living with HIV in Latin America, and it is estimated that between Latin America and the Caribbean, some 500 new HIV infections appear every day[49].

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[48] United Nations and World Health Organization (2009). *Situación de la epidemia de sida* (Publication ONUSIDA 09.36S, JC1700S) pp 80-84. Geneva, Switzerland
[49] *Ibid.*

In Mexico, the first cases of AIDS were reported in 1981. In 1983, 65 cases had been diagnosed, and by 2010 ~144 thousand cases of AIDS had accumulated. By then, Mexico had become the country with the third largest number of reported cases, after the US and Brazil[50]. However, the prevalence of HIV in the adult population is relatively low (0.37%), making it a case for a concentrated epidemic. It is concentrated in high-risk groups, with 15% prevalence in men who have sex with men (homosexual and bisexual), 12% in sex workers, and 6% in IV drug users, compared to the average 0.37% prevalence in the general population. In fact, more than 70% of all HIV cases occurred among these three high risk groups. It should also be mentioned that of the total number of cases diagnosed, 83% were men, while only 17% women. Of all AIDS cases in Mexico from 1983 to 2010, ~95% of cases were transmitted sexually[51].

Regionally speaking, most AIDS cases were diagnosed in Mexico City DFwith ~23 thousand cases as of 2010, Mexico State with ~16 thousand, Veracruz with ~13 thousand, and Jalisco with ~11 thousand (cumulative incidence of 263, 107, 179, and 156 per 100 thousand, respectively). These four states represent 45% of cumulative AIDS cases, while the other 28 states represent the remaining 55%[52].

The Mexican healthcare system has been able to stabilize AIDS mortality rates in the past decade, mainly due to structural and financial changes that have improved access and quality of care to HIV/AIDS patients. In 1986, the National AIDS Prevention Committee, *Comité Nacional de Prevención del SIDA* (CONASIDA), was formed, and with it the first attempts to establish criteria and provide funds for diagnosis, treatment and prevention. In its initial years, CONASIDA had no formal budget, and it functioned through external programs and resources. It was not until 2001 that it received its first federal resource allocation. However, in 2003 major federal resources started to flow into CONASIDA. With the creation of the *Seguro Popular*, and the fund for high-cost procedures and treatments FPGC (*Fondo de Protección contra Gastos Catastróficos*), HIV/AIDS was defined as one of the conditions that would be covered and treated, not only for *Seguro Popular* affiliates, but for any individual with HIV/AIDS who was not

[50] Instituto Nacional de Salud Pública. (2009). *25 años de SIDA en México. Logros, desaciertos y retos* (2nd ed.), pp. 101-120, and 303-314. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html
[51] *Ibid.*
[52] Izazola Licea J. A., Sucilla Pérez H. (2011). *Panorama epidemiológico del VIH/SIDA en México* [PDF file], CENSIDA, Secretaría de Salud, 1er Congreso Internacional en VIH e ITS, Monterrey, México

part of the Social Security system (IMSS, ISSSTE, etc.). As such, detailed definitions of prevention, diagnosis, and treatment procedures were catalogued in the CAUSES, such that it facilitated their use among the SSa and the SESAs. It should be mentioned that in order to gain access to FPGC funds, the *Consejo de Salubridad General* must first predefine whether a given condition or disease is considered catastrophic (from a financial perspective), and then provide and approve the guidelines of which categories of medical equipment and pharmaceutical are recommended for the inclusion in the CAUSES[53].

The FPGC progressively contributed to CONASIDA's budget, and to its operating arm CENSIDA. In 2004, CENSIDA covered 20% of HIV/AIDS expenses through the FPGC. In 2005, that portion became 60%. By 2006, the entire CENSIDA budget was contributed by federal sources through the FPGC, amounting to ~850 million Mexican pesos that year[54].

Including HIV/AIDS as one of the conditions to finance and treat through the FPGC was one of the great healthcare achievements that improved access and quality for patients. Through the FPGC, access to anti-retroviral therapies became universal in the Mexican healthcare system, and the access gap between the Social Security sector and that of the uninsured began to close rapidly.

It was also in 2003 that the Major Infrastructure Plan included the construction of 56 Ambulatory Centers for Treatment and Prevention of AIDS and Sexually Transmitted Diseases (CAPASITS). As of January 2012, there are 70 CAPASITS in Mexico[55], more than 90% of which have internet and telephone connectivity, and count with a robust management, logistics and monitoring IT system called SALVAR. These centers, with presence in every state of the country, are the primary prevention and treatment hubs of HIV/AIDS outside of the Social Security sector. It is through these centers that diagnosis, immunologic monitoring (through CD4+ T cell counts), viral load monitoring, and antiretroviral therapies are offered. Detailed diagnostic, monitoring and treatment guidelines are issued by CENSIDA. The CAPASITS follow these

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[53] Instituto Nacional de Salud Pública. (2009). *25 años de SIDA en México. Logros, desaciertos y retos* (2nd ed.), pp. 101-120, and 303-314. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html
[54] *Ibid.*
[55] CENSIDA, Secretaría de Salud. (2012). Directorio de *centros ambulatorios para la prevención y atención del SIDA e ITS (CAPASITS)* [PDF file]. Retrieved from http://www.censida.salud.gob.mx/interior/capasits.html

guidelines closely, including the CD4+ T cell count and viral load measurements every four months.

Currently, of those patients diagnosed through the CAPASITS who require antiretroviral therapy, it is estimated that 90%-95% are being covered. With financial backing of *Seguro Popular* and FPGC, and the operating arms of the CAPASITS, the SSa covered 52% of HIV/AIDS patients requiring antiretroviral therapies in 2008, followed by IMSS (40%), and ISSSTE (7%)[56].

Looking forward, there are several challenges to work on in the HIV/AIDS landscape of Mexico. Primarily, the reported prevalence of HIV in the country is an unreliable measure of the real prevalence. It is estimated that ~50% of the HIV positive individuals in Mexico are unaware of it[57]. The great challenge is to identify those thousands of Mexicans who currently have an asymptomatic infection.

Another important aspect is the fact that more than 40% of HIV detections are gathered in late stages of the infection, with patients already having AIDS-associated symptoms (in fact, the CAPASITS found that the average CD4+ T cell count in patients that were given their first ART prescription was ~90 cells/mm^3)[58]. Therefore, initiating antiretroviral therapy early becomes of crucial importance. Not only is it ideal to diagnose patients in early stages of the infection, but it is also important to initiate therapy as soon as possible when the patient is already in advanced stages.

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[56] Córdoba Villalobos J. A., Hernández Ávila M., Izazola Licea J. A., Magis Rodríguez C., García de León C., Hernández Tepichín G. (2009). *El VIH/SIDA en México 2009.* CENSIDA, Secretaría de Salud. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html

[57] Instituto Nacional de Salud Pública. (2009). *25 años de SIDA en México. Logros, desaciertos y retos* (2nd ed.), pp. 101-120, and 303-314. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html

[58] *Ibid.*

Chapter 3: Thesis Objectives and Methodology

Statement of Hypotheses, Purpose and Methods

Healthcare outcomes in Latin America will improve, I would argue, not only by spending more in healthcare, but by introducing efficiency oriented healthcare models that create low-end and new-market disruptions in the healthcare spheres.

Examples of such disruptive models in healthcare are already appearing. In the US, for instance, retail medicine centers such as CVS' Minute Clinics and Walgreens' Take Care Clinics, are changing the way in which patients satisfy their basic medical needs, hence disrupting the existing primary care physician practice. In Mexico, *Farmacias Similares* are implementing a similar retail medicine model that is disrupting the system, while recent start-ups like *Clínicas del Azúcar* are offering low-end disruptive models for the diagnosis, care and treatment of diabetes (which has reached epidemic proportions in Mexico) at the bottom and middle of the pyramid.

This thesis stems from the premise that disruptive innovations will not only impact healthcare delivery, but will also change the face of the device and diagnostics markets. Most medical devices and diagnostics in Latin America are based on US and Europe's traditional business models of "high-performance, high-ticket price" devices. While this approach has significantly impacted patients' lives, it mainly targets higher income brackets, or high-resource payer-provider sectors.

Point-of-Care (POC) diagnostics promise disruptive models in diagnostics that will increase access, enhance care, and help better allocate healthcare resources. In short, the concept of POC embodies the trade-off of lower quality (usually in the way of lower specificity and sensitivity), but offering much more accessibility and portability, at a significantly lower cost. POC promises typical low-end and new-market disruptions in medical diagnostics and devices.

Cambridge-based Daktari Diagnostics is one of such companies focused in POC diagnostics. It has developed a CD4+ T cell count diagnostic device for the management and treatment of HIV/AIDS patients. This device, which is significantly cheaper, more accessible, portable and faster (albeit with lower specificity and sensitivity) than the gold standard flow cytometers, promises to disrupt the current CD4+ T cell count market.

The objective of this thesis is to identify the unmet medical need, as well as the commercial feasibility and potential market size, for such CD4+ T cell count diagnostic in the Mexican HIV/AIDS market. This general objective has been divided in two hypotheses:

i) Given the present Mexican diagnosis and treatment model for HIV/AIDS, Point-of-Care CD4+ T cell count devices, illustrated by Daktari CD4, offer an alternative to flow cytometers for addressing an unmet medical need in the HIV/AIDS patient experience. *NULL: POC CD4+ T cell count devices, and thereof Daktari CD4, do not offer an alternative to flow cytometers for an unmet medical need in Mexico's HIV/AIDS current diagnosis and treatment paradigm.*

ii) There is a substantial unmet market demand in Mexico for POC CD4+ T cell count diagnostics that would be attainable with a POC diagnostic device like Daktari CD4. *NULL: There is insufficient potential market demand in Mexico for POC CD count devices, and therefore for Daktari CD4.*

These hypotheses will be evaluated and discussed on a preliminary basis, aiming not at statistical significance for each one of them, but rather at qualitatively uncovering some of the relevant aspects of a potential unmet medical need for POC CD4+ diagnostics in Mexico, as well as quantitatively estimating the size of such a hypothesized need. Through this process of preliminary evaluation of hypotheses, I expect to discern some generalizable lessons, trends, and opportunities in the field of *Point-of-Care* diagnostics in Mexico.

Review of Existing Literature

An extensive review of existing literature was performed in order to understand and address the medical need for Point-of-Care CD4+ T cell count diagnostics, and its potential

application in the Mexican health care market. This literature review became the foundation for exchanging ideas and discussing with industry, public sector and healthcare officials in Mexico. The literature reviewed included peer-reviewed journals in medicine, science, public health, business and economics, as well as presentations and documents from different Mexican and international institutions directly related to the field of HIV/AIDS.

Continuous interaction with Daktari Diagnostics' executive team, and use of their internal documents and presentations, provided valuable context and guidance within the space of Point-of-Care diagnostics, and their use in the management and treatment of HIV/AIDS. Current newspaper, internet and magazine articles also provided useful information regarding relevant developments in the field. In particular, the recent FDA approvals of both the Truvada preventive pill, and the OraQuick At-Home HIV tests were closely followed in the media and in scientific opinion reports.

International organization websites, especially those of UNAIDS and the WHO, served as valuable sources for epidemiological data, as well as for history and development of HIV/AIDS initiatives and programs on a global scale. The CENSIDA website offered unparalleled context on the Mexican healthcare system, and of the infrastructure and programs surrounding the management and treatment of HIV/AIDS in Mexico.

Interview Process and Selection of Interview Participants

In addition to an extensive literature review, direct interviews in Mexico were ultimately the primary source of context, information and guidance in identifying and understanding the medical need for POC CD4+ T cell count diagnostics in the Mexican healthcare market. The interviews conducted covered a broad spectrum of stakeholders in the Mexican HIV/AIDS landscape, from public sector officials and field practitioners, to healthcare industry executives and consultants **(see Figure 3-1).**

After gaining detailed understanding of the HIV/AIDS landscape in Mexico, a stakeholder map was developed, and an exhaustive, ideal list of interviewees was drafted. Having this map as a starting point, potential interviewees were recruited, whenever possible, through

professional and personal network contacts as well as through professors' and thesis advisors' contacts and suggestions. Whenever a networking route was not available, I attempted to directly reach potential interviewees via public sources of contact information (website and academic publication contact information). The former approach provided the majority of interviews, while the latter generated only a few responses that resulted in interviews. Ultimately, the finalized group of interviewees, while not resembling the ideal list of interviewees in either number or breadth, did however provide a relevant sample of stakeholders in the Mexican healthcare space and in the HIV/AIDS landscape. By including at least one institution and/or professional within each of the relevant stakeholders of the HIV/AIDS landscape in Mexico (i.e. private and public providers, payers and funding sources, physicians, patients and advocacy groups, regulators, government officials, NGOs, and direct and indirect private competitors), the interview sample became, if not representative, at the very least valuable and complete for shaping an educated interpretation of the need and potential for POC CD4 count diagnostics.

I recognize that this interview sample is not exhaustive, and that the process of selection of interviewees was not randomized. As such, I recognize that this represents a source bias in my understanding, and in my drawing of conclusions, of the medical unmet need for POC CD4+ T cell count diagnostics.

A Legatum Seed Grant, from the MIT Legatum Center for Development and Entrepreneurship, was instrumental in providing funding for conducting the previously mentioned interviews in Mexico.

It is worth emphasizing that the goal of these interviews was not to reach statistically significant conclusions, but rather to gather sufficient and knowledgeable impressions from stakeholders, to synthesize such impressions, and to extrapolate them into reasonable conclusions regarding the medical unmet need for CD4 count devices in particular and for POC diagnostics in general. I acknowledge that a larger study may be necessary to validate my conclusions, but I believe that the viewpoints obtained in the present study provide a reasonable perspective, and may serve Mexican and Latin American healthcare stakeholders in

shaping their views and policies regarding *Point-of-Care* diagnostics and disruptive innovation models for medical diagnostics and devices.

Figure 3-1: Organizations Represented, and Breakdown of Interview Respondents by Sector

Represented Organizations
• bioMérieux México (2)
• Abbott México (2)
• McKinsey & Company México (1)
• CENSIDA –nacional– (1)
• CENSIDA –nivel estado– (2)
• CAPASITS (3)
• Sanatorio La Luz –hospital privado– (2)
• Secretaría de Salud –nivel estado– (6)
• Seguro Popular (3)
• Laboratorio Estatal (3)
• Centro de Transfusion de Sangre –nivel estado– (2)
• Capsida ONG-(1)
• Amigos Contra el SIDA ONG (1)
• Primedic (1)
• Clínicas del Azúcar (1)
• HIV/AIDS focus physicians (3)
• Patients (6)

Pie chart breakdown:
- Government Organizations and Officials: 23%
- Patients and Advocacy Groups: 20%
- Public Providers and Physicians: 15%
- Industry: 13%
- Private Providers: 10%
- Funding Sources and Public Payers: 8%
- Other: 13%

Chapter 4: Primary Hypothesis #1: Point-of-Care CD4+ T Cell Count Devices, a Solution for an Unmet Medical Need

Understanding the Medical Need

There are two major avenues for identifying HIV patients in Mexico. The primary mechanism is by voluntary patient visits, and the secondary method is through laboratory exams performed in blood donations at blood banks. There are other mechanisms, like pregnancy physician control visits, but they account for a very small portion of the total number of cases.

Given the current epidemiologic picture of Mexico, it is common for voluntary visits to come from patients belonging to one of the high risk groups: men who have sex with men, sex workers (men and women), or intravenous drug users. These three groups alone account for more than 70% of all accumulated cases of HIV in Mexico[59]. Also, it is not uncommon for these patients to seek attention in the later stages of the disease, when there may be already some signs of AIDS. From interviews conducted, it is estimated that between 60% and 70% of all voluntary visits are already in late stages of infection.

Laboratory exams done on blood donations at blood banks are another avenue for identifying HIV patients, and the primary one for patients who do not belong to (or engage with persons from) any of the high risk groups. Actually, blood banks almost exclusively detect patients who do not belong to high risk groups. This is not particularly surprising given that homosexual and bisexual persons, IV drug users, sex workers, and even "promiscuous heterosexuals" are not allowed to donate blood in Mexico. While a small minority may do so, the overwhelming majority of high risk groups do not donate blood in Mexico.

There is a predefined protocol for approaching and contacting identified patients through blood banks, and for these patients to undergo further diagnosis and treatment. There

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[59] Izazola Licea J. A., Sucilla Pérez H. (2011). *Panorama epidemiológico del VIH/SIDA en México* [PDF file], CENSIDA, Secretaría de Salud, 1er Congreso Internacional en VIH e ITS, Monterrey, México

is a correlation between donating blood and belonging to the social security system. Therefore, most of these patients follow-up and seek treatment primarily through the IMSS or ISSSTE[60].

On a related note, it is worth mentioning that Mexican health authorities believe and estimate that between 40% and 60% of people currently infected with HIV in Mexico do not know it, and that a significant portion of them may already require ART[61].

The potential for POC CD4 count diagnostics is very limited in the traditional social security system. HIV patients with access to the IMSS, ISSSTE, and the like, are located primarily in urban areas. Many of the diagnosing and treating hospitals of these patients have sufficient capital and equipment for conducting, on site, the required diagnosis, control and treatment steps. Flow cytometers are commonly found in these hospitals' laboratories and, whenever they are not, the urban setting allows for samples to be taken to other nearby laboratories. Equally important, the urban location of the patients themselves takes away the urgency of obtaining laboratory results and information at the point-of-care; the patient can always communicate with the hospital and even repeat a visit with minor inconvenience. It is not uncommon for patients to receive their CD4 counts and viral loads within a day of their visits, particularly in the cases when AIDS-associated symptoms are already visible.

The previously described setting was observed first hand during hospital visits in Mexico, and similar conclusions were drawn. Interviewees with health professionals and patients, as well as with members of other providers, payers, and government organizations and officials, were unanimous in recognizing no relevant medical need for POC CD4 counts within the setting of the Mexican social security institutions. There are, however, some minor areas where I believe POC CD4 count devices could have an impact within the IMSS, but they are limited in scope and in number.

It is, therefore, reasonable to say that there is little to no medical need that is currently being unmet by the standard of care in these institutions. POC CD4 count devices in general, and Daktari's CD4 in particular, would not provide an alternative solution to an identified

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[60] Izazola Licea J. A., Sucilla Pérez H. (2011). *Panorama epidemiológico del VIH/SIDA en México* [PDF file], CENSIDA, Secretaría de Salud, 1er Congreso Internacional en VIH e ITS, Monterrey, México
[61] Instituto Nacional de Salud Pública. (2009). *25 años de SIDA en México. Logros, desaciertos y retos* (2nd ed.), pp. 101-120, and 303-314. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html

medical need, but rather would constitute an inferior laboratory and clinical proposition, competing head-to-head against an established protocol, a medical practitioners' consensus, and a strong group of medical device and diagnostics companies.

Similarly, there is little opportunity to satisfy a medical need through IMSS-Oportunidades (or IMSS-O). However, this does not necessarily mean that there could not be an opportunity in the future. The lack of medical need is primarily due to how IMSS-O is set-up structurally, and to the kinds of medical services that it provides. As a federally funded, IMSS-managed institution, IMSS-O offers very basic medical care in rural areas, focusing on general ambulatory medicine and on maternal and neonatal services. IMSS-O does not offer HIV related diagnosis, control or treatment options, nor does it have the financial backing or stability if it were to pursue HIV-related efforts. Furthermore, its health professionals have little familiarity with HIV diagnosis, control or treatment. In fact, whenever there are patient cases where the clinical presentations exceed general ambulatory medicine or basic maternal and neonatal needs, the patient is typically referred to the nearest SSa and SESAs of the respective state, regardless of whether this patient is covered by the Seguro Popular umbrella.

Nonetheless, it is estimated that IMSS-O keeps (or should keep) responsibility for some 5-6 million people who are not currently covered under the Seguro Popular system[62], yielding some potential ~20,000 HIV patients, assuming average prevalence rates. The capital-deprived, rural nature of their service makes IMSS-O an apparently ideal candidate for POC diagnostics, not just for CD4 counts but for many other types of POC diagnostics. However, it remains a structural question whether IMSS-O (and its funding sources) wishes to expand the type of health coverage it provides, and therefore offer the potential for using POC diagnostics in the future. For now, it suffices to understand that while the medical need is present, a real opportunity is very limited and only hypothetical at the moment.

For HIV patients currently under the IMSS-O umbrella, there are four available avenues for diagnosis, control and care of disease. The first one is the possibility of IMSS-O enhancing its healthcare offering. The second one is the referral to the SSa and SESA centers, whether the patient is yet covered or not by the Seguro Popular (this is the more common scenario). The

[62] Chertorivski-Woldenberg S. (2011). Seguro Popular: logros y perspectivas. *Gaceta Médica de México, 147,* 487-496

third one is for the SSa and SESAs to reach out to the patient, and eventually substitute the role of the IMSS-O, through decentralization efforts and programs (i.e. opening new CAPASITS, having ambulatory programs, etc.) for which there is already some precedent. Finally, the patient could go on undiagnosed and/or eventually untreated for HIV, which is not entirely unprecedented.

All interviewees, with the exception of one NGO representative, were unanimous in dismissing IMSS-O as a relevant source of a care for HIV/AIDS patients and an organization for providing POC CD4 count diagnostic alternatives. The six patient interview responses were excluded from this matter, since I deemed them lacking the context to from a well-informed opinion. Most non-patient interviewees (28 out of 34 interviewees) identified the unique position of IMSS-O as a model through which POC devices could be introduced in theory, and nearly all of them (27 out of the 28 interviewees that identified this unique position) noted the structural and funding limitations of IMSS-O as the primary obstacle for any POC CD4 count to become a reality through IMSS. Some interviewees (2 out of 34), went as far as claiming it "impossible" for IMSS-O to adopt POC CD4 count diagnostics.

All of this is to say that the major avenue of attention for HIV/AIDS, as well as the primary source of medical opportunity for POC CD4 count diagnostics, is found in the SSa and SESAs through the operating arms of the CAPASITS. In short, there is a clear and relevant opportunity through the CAPASITS, by both complementing the current services and by expanding them even further. Before assessing the applicability of POC CD4 count diagnostics at the CAPASITS, and understand the core of the medical need, it is important to first describe the typical HIV patient experience.

Diagnosis and Treatment at the CAPASITS: Honing in on the Unmet Need

As the operating arms of CENSIDA, the CAPASITS are the main points of contact with HIV patients. For all intents and purposes, the CAPASITS are the focal point of attention for any POC CD4 diagnostics that may be implemented in Mexico, and in them resides the primary medical need. All CENSIDA and CAPASITS interviewees (6 in total) expressed interest and enthusiasm for

POC CD4 count devices, and for the potential implementation in the future. Most interviewees (the 6 out of 6 CENSIDA and CAPASITS interviews, the 31 out of 34 other interviews, making it a total of 37 out of 40) identified, in general, the CAPASITS as the primary targets and sources of oportunity for POC CD4 count devices.

There are currently 70 CAPASITS in Mexico (as of January 2012), with presence in every state of the country **(see Figure 4-1)**. A typical CAPASITS has at least two and up to four physicians (one of whom is the director of the center), three fourths of whom are general practitioners and about one fourth specialists in internal medicine or infectious diseases. The centers also have at least one nurse phlebotomist or other type of general practice nurse, a resident psychologist, a social worker, and at least one person performing administrative tasks. It is not uncommon to find additional support staff that is usually involved in, among other things, HIV/AIDS education and prevention programs. ELISA HIV diagnostic tests, blood sample collection supplies, and all antiretroviral drugs are kept in stock (refrigerated when needed) in the CAPASTIS. More than 90% of CAPASITS have telephone connectivity and internet connectivity, which allows them to enter the national IT platform SALVAR, *Sistema de Administración, Logística y Vigilancia de Antiretrovirales*. For sample pictures of a typical CAPASITS, refer to **Appendix B.**

The interaction with HIV patients usually begins through one of three avenues: a voluntary patient visit (>90% of cases), a referral of an already diagnosed HIV patient (<5% of cases), or a proactive campaign done, for instance, at universities, prisons, or places with populations at high risk like IV drug users or homosexual communities (<5% of cases). The voluntary patient visit illustrates the most common interaction and patient experience.

When the patient visits the CAPASITS, the first step is to conduct a consultation with a resident physician. During this consultation, the physician reviews many aspects of the patient, including clinical history, risk factors, prescriptions and medications, substance abuse, sexual practices, and social history. The consultation is followed by a thorough physical examination. The guidelines for the patient visit and physical exam are all detailed and published by CENSIDA, and are updated on a yearly basis. These guidelines are not only followed by

CAPASITS as good guides for the patient visits and physical exam, but they also serve as updates to ARTs and related HIV literature for many physicians.

Figure 4-1: Locations of CAPASITS in Mexico[63]

An initial HIV diagnostic test is then performed, using a portable rapid test. Lately, the more commonly used on-site test in the CAPASITS is the Trinity Biotech's Uni-Gold Recombigen HIV rapid test. If the test result is positive, which is found out after 10-15 minutes, a small blood sample is taken, and a confirmatory ELISA (enzyme-linked immunosorbent assay) test is ordered at an off-site laboratory. If the ELISA test is also positive, then finally a Western blot is done at the same laboratory, to make a final confirmation.

Both of these tests, the ELISA and the Western blot, are done off-site the CAPASITS. Usually, they are done at the respective State Laboratory, although in a minority of CAPASITS

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[63] CENSIDA, Secretaría de Salud. (2012). *Directorio de centros ambulatorios para la prevención y atención del SIDA e ITS (CAPASITS)* [PDF file]. Retrieved from http://www.censida.salud.gob.mx/interior/capasits.html

(~10%), where there is no State Laboratory infrastructure, samples are sent to a central laboratory in Mexico City.

Meanwhile, the patient in asked to return to the CAPASITS two days after the rapid HIV test is done (if there is a State Laboratory), or seven to ten days later (if the sample is sent to Mexico City). This is a clear inconvenience for patients, especially for those who live far from the CAPASITS, to have to leave and return again to the CAPASITS. There is some patient attrition at this point, but it is minimal. Although data and behavioral statistics are scarce, it is estimated at the CAPASITS that there is less than 5% attrition at this point[64].

The patient then returns to the scheduled appointment, and at this point the results from the confirmatory HIV tests are available. The patient again undergoes a consultation with a resident physician, which includes another physical exam and a review of the patient's medical history. This consultation is, among other things, used to indicate the urgency with which the patient must be seen again. If there are AIDS-associated symptoms, or other clinically relevant observations that suggest a poor medical condition, the patient is scheduled an appointment within 1-2 weeks. If the patient's condition is not alarming, then the appointment is scheduled in four weeks time.

This consultation is followed by a phlebotomist nurse (or by whichever nurse is resident at the CAPASITS) taking a blood sample by venipuncture. The sample is taken, named and codified, and kept in an ice-box until sent to the State Laboratory (or to Mexico City in some cases) along with all other samples taken that day and shipped at noon. This sample is used for two relevant tests: a CD4+ T cell count test done by flow cytometry, and a viral load (VL) test using PCR (polymerase chain reaction).

After the sample is taken, the patient follows with visits with the social worker and the psychologist, thus setting the behavioral groundwork for a life with HIV and, most probably, with ART.

As previously mentioned, the patient is scheduled a third appointment to the CAPASITS, yet again inducing patient attrition, particularly among patients that live a long distance from the respective center. Directors of CAPASITS, and officials of CENSIDA, are aware of the patient

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[64] Chacon J., Diaz R., Murillo, personal communication, July 2012

attrition that is created from this "back and forth" of patient visits, however there is little documentation or data analysis on this respect. The belief, although not very well supported, is that some ~10% attrition occurs where patients never visit again the CAPASITS[65]. The more relevant impact, however, is observed in patients consistently lengthening the time between scheduled visits, often time missing appointments by several months. Considering that the majority of (60%-70%) of visiting patients to the CAPASITS are already in late stages of the disease (AIDS-associated symptoms), this attrition and/or significant time in between visits usually represents a delay in starting antiretroviral therapy.

The patient's third visit is crucial. At this point, results for the CD4+ T cell count and viral load are known. While both measures, the CD4+ count and the viral load, are taken, it is the CD4+ count that determines whether a patient is immunosuppressed and should start ART[66]. The World Health Organization recommends initiating ART at CD4+ T cell counts of 350 cells per mm^3 or below[67]. It is not uncommon, however, for some health practitioners and health policy officials to suggest initiating ART at or below counts of 200 cells per mm^3. Nonetheless, recent scientific data, showing markedly decreased transmission of disease and reduction of clinical events when ART is begun earlier[68], has made the ≤350 cells/mm^3 the more accepted standard of ART initiation worldwide. Mexico's CENSIDA guideline, which is followed closely by the CAPASITS, indicates initiation of ART with CD4+ counts of ≤350 cells/mm^3 or when CD4+ counts are "close to this number" coupled with identifiable symptoms. Advanced AIDS-associated symptoms usually trigger ART, irrespective of CD4 cell count (although they almost never occur at high CD4 cell counts)[69].

Consequently, the CD4+ count is the main observation made during the patient's third visit. If counts are above 350 cells per mm^3, the patient is asked to visit the CAPASITS every four months thereafter. If counts are ≤350 cells/mm^3 (or close to this number in addition to serious

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[65] Chacon J., Diaz R., Murillo, personal communication, July 2012

[66] Kumar V., Abbas A. K., Fausto N., Aster J. (2010). Chapter 6: Diseases of the Immune System – Secondary Immunodeficiencies, *Robbins and Cotran Pathologic Basis of Disease* (8th ed). Philadelphia, PA: Saunders

[67] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1),* pp. 45-54

[68] Cohen M. S. *et al.* (2011). Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *The New England Journal of Medicine, 365 (No 6),* pp. 493-505

[69] CENSIDA, Secretaría de Salud. (2012). *Lineamientos para el tratamiento antirretroviral de personas con VIH para instituciones del sistema nacional de salud* [PDF file]. Retrieved from http://www.censida.salud.gob.mx/

clinical presentation), the ART is initiated. The choice of ART drugs is guided by multiple variables involving the patient's condition and clinical case (i.e. pregnancy, neurological disease, depression, and other contra-indications). For the purpose of this discussion, it is not necessary to delve into the details of how these choices of ART are made, but it must be mentioned that it is an important and pivotal point in the patient's disease management.

Once ART is initiated, the patient is expected to visit the CAPASITS every month for the first year, and every two months in subsequent years, during which visits the associated ART in renewed. All throughout this follow-up, CD4+ T cell counts and viral loads are measured every four months (following the same on-site venipuncture procedure, and blood sample shipment previously explained), and used as relevant indicators for ART management. At this stage, the CD4+ counts become second in relevance to the viral loads, which are the primary measurements of ART success or failure. A very low (i.e. undetectable) VL is the main sign of ART success, while detectable and higher VLs are signs of ART failure, at which point ART is reassessed and changed. CD4+ T cell counts are helpful for understanding the level of immunosuppression a patient might have, but they are not the more relevant measurement at this point[70]. Again, while the choices of ART regimen combinations are clinically essential for HIV patient management, the associated details are not necessary for the purpose of this discussion. It suffices to say that i) viral loads, and not CD4+ counts, are the primary decision indicators, and that ii) CD4+ counts are, in any case, always measured for complementary information.

As expected, the patient experience for referrals and proactive campaigns (both accounting for less than 10% of cases) are similar to the voluntary visits, with either fewer steps or altered details. A referral almost always comes with a confirmed Western blot diagnosis in the medical history, making the patient's first visit the one where CD4+ counts plus VLs are ordered (i.e. the standard "second visit"). Proactive campaigns usually consist of rapid HIV tests and, for those positive results, blood samples for ELISA and Western blot confirmations. The patient is then asked to visit the closest state CAPASITS for the standard "second visit" where CD4+ counts and VLs are ordered. On some occasions (and always the case in prisons), there

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[70] CENSIDA, Secretaría de Salud. (2012). *Lineamientos para el tratamiento antirretroviral de personas con VIH para instituciones del sistema nacional de salud* [PDF file]. Retrieved from http://www.censida.salud.gob.mx/

are patients with already a positive diagnosis, and blood samples are taken for the purpose of obtaining CD4+ counts and VLs. **See Figure 4-2** for a graphic representation of the patient experience.

After understanding the typical experiences of HIV patients, the unmet need for POC CD4+ diagnostics immediately becomes apparent, even without discussing any economic advantages. Medical and administrative staff at CAPASITS observed the medical need, just as officials did at the state level Secretary of Health and the Seguro Popular. From a centralized perspective in CENSIDA, the need also became apparent, not only to solve a current medical need, but also to serve a future strategic need of reaching other regions and populations.

Figure 4-2: Diagnosis and Treatment Flow for a Voluntary Patient Visit
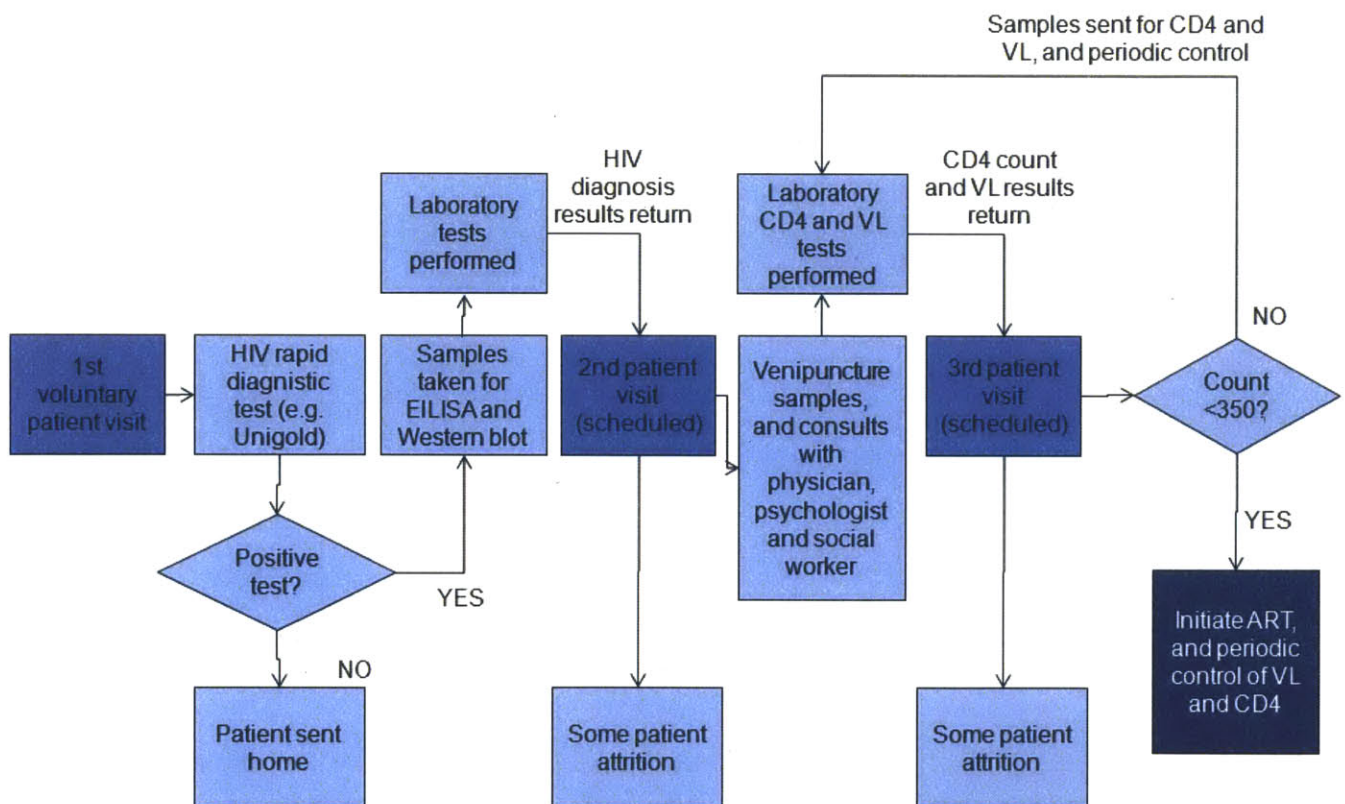
The core of the medical need for POC CD4+ counts, and therefore for a device with the characteristics of Daktari CD4, can be segmented in three areas or points of application, in decreasing order of medical need:

- i) Off-site use during proactive campaigns, both with patients already diagnosed and with patients whose HIV rapid test is positive.

- ii) Immediate use for CD4+ T cells count measurements at the point-of-care during the CAPASITS visits *before ART* has been initiated, thus decreasing potential attrition and speeding up the initiation of antiretroviral therapy.

- iii) Substitute use of follow-up CD4+ counts *after patient has initiated ART*.

The interviews conducted were instrumental in both helping identify each segment of need, and in shaping the preliminary evaluations of the relevance of each segment of need. Points of view from all sectors and organizations **(see Figure 3-1)** were taken into account for identifying the three sectors of need. However, for evaluating each segment of need, only the organizations that are directly or indirectly involved in the CAPASITS patient experience were considered as pertinent points of view. More explicitly, the CENSIDA (3), CAPASITS (3), Seguro Popular (3), Laboratorio Estatal (3), Centro de Transfusión de Sangre (2), Abbott Mexico (2), Secretaría de Salud (6), and HIV/AIDS Patients (6) interviews (corresponding to 28 out of the total 40 interviews) were the basis for preliminarily evaluating each segment of need.

The first segment of need is that of off-site use during proactive campaigns. Currently, HIV patients found through campaigns represent less than 5% of all CAPASITS cases, making it a small segment of present need. Nonetheless, the applicability of a POC diagnostic device (for instance, a Daktari CD4 device or its competitors) test is very clear in this segment, and the potential for escalation in also very tangible. Substituting completely the use of flow cytometry tests when in campaigns is certainly more probable than in voluntary visits to CAPASITS. This observation stems both from the importance of obtaining immediate CD4+ count information at the campaign site, and from the difficulty of taking and shipping blood samples while in campaigns. Furthermore, the nature of campaigns may vary in the future, from the current sporadic (3-6 times a year) campaigns done by each CAPASITS in specific high risk sites, to more consistent satellite location "mobile CAPASITS" in remote locations of each state.

This off-site campaign use may not only improve access, decrease attrition, and speedup ART initiation, but it may also become an important strategy for increasing the base of patients being diagnosed and treated, therefore helping identify the portion of patients who do not know yet they are HIV positive.

Out of the pertinent interviews, the great majority (27 out of 28) observed this segment of need as one were POC CD4+ count devices could have a significant impact. Only one interviewee (i.e. one of the six interviews at state Secretarías de Salud) stated there was no clear opportunity for POC CD4 count devices, claiming that a further centralized model, with improved laboratory infrastructure and sample transportation logistics, would be the solution to serving HIV/AIDS patients in marginalized rural areas. All other interviewees emphasized the importance of decentralizing efforts, and of creating access by providing POC solutions.

More importantly, 23 out of the 28 interviewees recognized that the lack of POC diagnostic ability in off-site campaigns as a key reason why off-site campaigns only represent a small (<5%) portion of all HIV/AIDS cases in the CAPASITS. Were there diagnostic means for identifying at the POC those patients who require ART urgently, interviewees considered, the number of off-site campaigns would increase in frequency and in impact.

The second segment of need is particularly relevant, because it represents a higher potential number of POC tests. By allowing for a rapid (~10-minute) CD4+ count measurement at the CAPASITS, the patient could be initiated with ART immediately. As opposed to waiting for laboratory results for approximately one month, beginning ART immediately could presumably decrease patient attrition and certainly improve patient outcome. Especially because most (~60%) patients are already in advanced stages of the disease, any improvement in ART initiation will result in a better patient prognosis, significantly fewer number of adverse clinical events, and a drastically decreased risk of transmission to other members of society[71]. A better prognosis also means fewer hospitalizations and associated symptoms during the time the patient waits for CD4+ count results, not to mention those patients who never return to the CAPASITS for their results. The benefits associated with decreased risk of transmission are also self-evident.

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[71] Cohen M. S., *et al.* (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *The New England Journal of Medicine, 365 (No 6),* pp. 493-505

The potential use of POC CD4+ count devices in general, and of devices like Daktari CD4 and its POC competitors in particular, for this segment of need may be of a complement or of a substitute nature.

In the complement scenario, CD4 counts are taken by a POC CD4 count device (like Daktari or its competitors), but also venipuncture samples are taken and samples are sent to State Laboratories for flow cytometer CD4 counts and for viral load tests. However, the low POC CD4 counts measured would be taken as indicators to immediately initiate ART. "Border line" and high CD4 counts would simply be recorded, while flow cytometer CD4 counts from central labs would be awaited as the relevant measurements for initiating ART. Follow-up visits every four months would have a similar approach to the measurements taken.

In the substitute scenario, phlebotomist samples would not be taken at all, and the viral load test would be completely omitted. In this case, no longer are samples shipped, but rather ART initiation and ART follow-up would be conducted via POC CD4 count tests alone (using Daktari or its competitors).

It is unlikely that substitute scenarios emerge in the CAPASITS that have State Laboratories close by. However, it would be a plausible alternative for those CAPASITS that are distanced from their State Laboratories, or for those that must send their samples to a central Mexico City laboratory.

For either complement or substitute scenario to be plausible, current CENSIDA guidelines for diagnosis and treatment would need to be modified, and different standards of sensitivity and specificity (to be discussed later) would need to be accepted. The likelihood of one scenario emerging versus the other is also affected by whether the CAPASITS in question has access to a State Laboratory or if it must send samples to a Mexico City central location; the latter case of course being more likely to have a substitute approach.

With regards to the applicability of POC CD4 diagnostics during CAPASITS patient visits, 24 out of 28 interviewees viewed it as a possibility, while 20 out of 28 viewed it as probable to happen within 1-4 years. Of the 24 who viewed POC CD4 count devices as a possibility, the overwhelming majority (22 out of 24) supported a complement scenario rather than a substitute scenario where venipuncture samples are no longer taken. When questioned about

this particular opinion, two arguments emerged as the main supports for complement versus substitute: i) those states without central laboratories are already moving towards investing in central laboratory infrastructures. Therefore, sending samples to "far away" laboratories will no longer occur within a few years. ii) Furthermore, not having venipuncture samples taken was a major concern because viral load tests would no longer be available. The scenario of having only CD4 counts as the basis for evaluating an already initiated ART was not welcome; delayed ART initiation and potential patient attrition was preferred.

To this end, the question was asked of whether a substitute scenario could be plausible *if POC viral load devices were also available* (that is, samples would not be sent to laboratories, but both CD4 count and VL could be determined at the POC). In this case, there was more acceptance (17 out of 24) of such hypothetical substitute scenario, with the caveat of sensitivity and specificity questions. While discussing the medical need and economic potential of POC viral load devices is beyond the scope of this thesis, it is important to understand that their introduction into the HIV/AIDS landscape positively affects the potential for POC CD4 count devices like Daktari and its competeitors.

Finally, the third segment of need is the one with the least medical need for POC, but at the same time the segment where the most tests are done. For economic reasons, this segment is perhaps the more straightforward to apply a POC diagnostic like Daktari CD4.

After ART is initiated, the viral load is the primary measurement used by physicians to evaluate efficacy of the therapy. While CD4 counts are also measured, they provide additional, although not vital, diagnostic information. Therefore, one would expect that the level of accuracy (i.e. sensitivity and specificity) required for CD4 counts at this point becomes less relevant than at the point of ART initiation. Therefore, the possibility of using POC CD4 counts (instead of flow cytometry CD4 counts) for follow-up and control measurements becomes more of an economic and convenience question than a medical one. It would not be surprising if these follow-up CD4 measurements become completely substituted by POC diagnostics (like Daktari CD4 or its direct competitors), assuming of course that they represent an economically sound alternative when compared to standard flow cytometers.

For this segment of need, the more relevant interviews were those of physicians (3), CAPASITS (3), and CENSIDA (3). While the opinion of other interviewees was also taken into account, the previously mentioned interviewees represent the gatekeepers of ART decisions and patient management. For this group of interviewees, most of them (8 out of 9) mentioned they would consider using POC CD4 counts instead of flow cytometry for the follow-up CD4 counts after the patient has initiated ART. However, 2 interviewees at CENSIDA, and 1 physician said that "detailed evaluations" should be conducted before making such decisions, but all agreed that in practice, CD4 counts were not used much for deciding efficacy of ART.

In short, there exists a relevant unmet medical need for point-of care CD4 count diagnostics in the operation of CAPASITS centers. This unmet need can be segmented into three needs.

The first one, the off-site testing during campaigns and "mobile CAPASITS" units, is a need stemming from the lack of laboratory infrastructure at campaign sites, and the need for immediate CD4 count feedback so that patients can be promptly initiated in ART. This is the personification of a POC diagnostic need. Currently, this segment represents less than 5% of all patient cases, but as suggested by interview responses, the application of POC CD4 diagnostics may actually increase size of this segment of need.

The second unmet need, that of CD4 counts for HIV patients who have not yet started ART, stems from the desire to decrease attrition in visiting patients to the CAPASITS, and from the need to accelerate ART initiation in patients that urgently require it. The benefits are primarily seen in decreased transmission of disease, as well as decreased clinical events that may results in poor prognosis and in misuse of economic resources in medical complications that could have been prevented with early ART. While several versions of solutions for this segment of need may emerge (complement versus substitute scenarios), the more likely scenario is that of the use of POC CD4 count devices at the CAPASITS, in addition to taking venipuncture samples and sending them to the lab. The probability of a substitute scenario, where venipuncture samples are no longer taken, is affected, among other things, by the introduction of more POC diagnostics like viral loads.

Finally, the third unmet need is barely a medical need. While obtaining CD4 counts after ART is initiated is part of the treatment and management protocol, at this point the accuracy of CD4 counts is not as relevant as during initiation of ART. Therefore, the tradeoff of a lower specificity and sensitivity POC CD4 count test that is simpler, faster and cheaper than the flow cytometer standard, can now be easily evaluated.

The "Quality" versus "Convenience" Tradeoff

At the core of any point-of-care diagnostics discussion a fundamental healthcare question emerges: should "quality" (usually in the form of specificity and sensitivity) be sacrificed in exchange for "convenience" (typically in the form of affordability, simplicity and access)? Unlike the traditional diagnostics innovations that keep one characteristic constant while improving the other (i.e. better performance at the same cost, or same performance at a lower cost), POC diagnostics usually face a tradeoff between two characteristics that are difficult to compare against one another. This difficulty rests on the observation that, in diagnostics, "quality" indicators are measurements of patients' health outcomes, while "convenience" indicators are usually measurements of economic and human resources.

A sensitive test means few patients with disease will be undetected, and therefore suffer the consequences of being untreated (or facing delayed treatment). A specific test means few patients will be miscategorized as infected, and therefore unnecessarily suffer the risks and side effects of treatment. High specificity and sensitivity means better health quality.

A cheaper, faster, simpler, and/or more easily accessible test means, in essence, freeing up economic and human resources. More physical capital and financial resources are therefore allocated to other objectives, and more human capital is free to serve other needs.

POC diagnostics, by definition, must therefore compare and contrast dollars to health outcomes. POC diagnostics force oneself to ask the question: how much is a given health outcome worth? This fundamental question has always been at the core of health care and policy, and this is certainly not the first time this question has been raised or analyzed.

However, it still is, and will continue to be, a crucially relevant question to ask and debate whenever facing healthcare innovation choices.

The last few decades have seen the question of controlling ever-rising healthcare costs become of paramount importance. To address this question, health academics, policy makers, and the like, have developed and contributed to an expanding field of cost-effectiveness health research. The application of cost-effectiveness principles and estimates (in which a variety of economic measurements are made in order to evaluate and compare the costs and benefits of health outcomes), is slowly becoming a very helpful tool and decision aid for health policy[72].

Approaches to evaluating both direct and indirect costs of diseases are becoming more and more standardized. There is also growing acceptance of the use of quality-adjusted life years (QALYs) as one of the measures of disease burden[73], and growing consensus in the assignment of QALYs to a broad array of diseases and conditions. The QALY methodology, it should be mentioned, assigns a year of perfect health a value of 1.0, and death a value of 0.0. Years that are not lived in full health (disease, loss of a limb, etc.) are assigned values between 0.0 and 1.0[74].

Cost-effectiveness measurements are helpful for comparing two or more interventions or approaches to the same condition or disease, or even at times, across diseases or conditions. A particularly helpful comparison is one where the incremental costs of a given intervention are compared to the number of quality-adjusted life years that it yields (vis-à-vis a baseline scenario), or incremental cost per incremental QALY[75]. That cost per QALY then serves as a decision aid in determining whether a certain procedure is considered not cost-effective (e.g. incremental US$300,000 per additional QALY), possibly cost-effective (e.g. US$50,000 per QALY), or absolutely cost-effective (e.g. US$5,000 per QALY). While assignment of dollar value

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[72] Grosse S. D., Teutsch S. M., Haddix A. C. (2007). Lessons from Cost-Effectiveness Research for the United States Public Health Policy. *The Annual Review of Public Health, 28,* pp. 365-391

[73] Berndt E. MIT Sloan School of Management.(2012). *From efficacy to effectiveness to cost effectiveness.* [PDF file]

[74] National Institute for Health and Clinical Excellence (NHS). (2010). *Measuring effectiveness and cost effectiveness: the QALY.* Retrieved from http://www.nice.org.uk/newsroom/features

[75] Grosse S. D., Teutsch S. M., Haddix A. C. (2007). *op. cit.*

thresholds could be considered arbitrary, there is growing consensus among academics and policy makers around the values of these benchmarks[76].

All of this is to say that cost-effectiveness, in addition to efficacy and quality, is an important area to be considered by health officials and regulators when evaluating the potential use of POC diagnostics. Cost-effectiveness indicators, like incremental cost per incremental QALY, should arguably be at the center of attention for understanding the impact and relevance of POC diagnostics.

It is not the purpose of this writing to conduct cost-effectiveness analyses comparing flow cytometers to POC CD4 count diagnostics in general, or Daktari CD4 in particular. Such comparisons are complex and often require probabilistic modeling and robust sensitivity analyses. While deserving on their own, such approaches are beyond the scope of this thesis. Nonetheless, it is important to have introduced and mentioned cost-effectiveness as a helpful tool for evaluating the quality versus convenience tradeoffs that POC diagnostics embody in their value proposition.

Returning to the notion of measuring quality, I note that standard flow cytometer technologies are considered the gold standard for CD4 T cell counts. Devices like Becton Dickinson's FACSCalibur or Beckman Coulter's EPICS XL/MCL are usually taken as the standard against which other CD4 count diagnostics are compared. As such, flow cytometry diagnostic accuracy is a misleading term, as there are no practical ways to test the diagnostic accuracy of flow cytometers. For all intents and purposes, devices like FACSCalibur and EPICS XL/MCL can be considered to have 1.0 sensitivity and 1.0 specificity for measuring CD4 T cell count around a predefined threshold, like 350 cells/mm^3 or 200 cells/mm^3.

In reality, physiological variation of CD4 counts is observed in HIV positive and HIV negative patients (for instance, CD4 counts lower in the morning than in the evening, or variations related to exercise and smoking). Such physiological variations certainly account for more than the technical measurement variability that standard flow cytometry devices may present[77].

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[76] Berndt E. MIT Sloan School of Management.(2012). *From efficacy to effectiveness to cost effectiveness.* [PDF file]
[77] WHO. (2010) *Technical Brief on CD4 Technologies* [PDF file}. World Health Organization. Retrieved from www.who.int/diagnostics_laboratory

In any case, measures of accuracy of new CD4 count technologies are evaluated by comparing results generated by the new test with those obtained for the same samples using a reference technology. Three measures of accuracy are frequently used: i) correlation and linear regression analyses, ii) bias, and iii) misclassification.

Correlation coefficients are frequently used, but, on their own, do not indicate the level of agreement. For instance, obtaining consistent high levels of misclassification, despite excellent correlation, is a clinically relevant problem. Bias reflects the average difference between the results of the new technology and reference technology[78].

Bias is usually reported using Bland-Altman, wherein the difference between the two methods is plotted against their mean. If the differences do not vary systematically over the range of CD4 counts studied, then the overall mean can be calculated and bias can be indicated. However, in most new technologies, the magnitude and variability of the differences are almost always larger at higher counts, making the bias variable across ranges. Furthermore, whether the differences are normally distributed can be evaluated statistically, in which case 95% of the differences will lie within two standard deviations. This distribution is referred to as the "limits of agreement" or LOA. It has become a standard in the literature to evaluate LOA ranges of $\leq$200 cells/mm^3 as excellent method agreement, $\leq$300 cells/mm^3 as acceptable, and >300 cells/mm^3 as imprecise[79].

Finally, misclassification probabilities describe the likelihood that a new test will classify a measurement either higher or lower than a given threshold value. These probabilities are the equivalent of sensitivity and specificity, and they are clinically relevant[80]. For instance, a Daktari CD4 upward classification of samples that actually had CD4 counts below 350 cells/mm^3 (using reference technology), would be a false negative, leading to a delay in ART. Analogously, a downward classification of samples that actually had CD4 counts above 350 cells/mm^3 (using reference technology), would be a false positive resulting in premature ART. One important disadvantage to misclassification probabilities is that they do not differentiate between high-

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[78] WHO. (2010) *Technical Brief on CD4 Technologies* [PDF file}. World Health Organization. Retrieved from www.who.int/diagnostics_laboratory
[79] *Ibid.*
[80] *Ibid.*

magnitude inaccuracy (e.g. a test count of 100 when the actual count was 355) and low-magnitude inaccuracy (e.g. a test count of 345 when the actual count was 355). A more important measurement, given its clinical relevance, might be the probability of a true CD4 count <250 cells/mm^3 being misclassified as >350 cells/mm^3. Unfortunately, these comparisons are rarely explicit in CD4 count technology publications[81].

Daktari's CD4 prototype study, conducted at the Massachusetts General Hospital in Boston, recruited 49 HIV positive patients and 4 HIV negative patients. The reference CD4 count measurements were conducted using Becton Dickinson's FACSCalibur. Using Passing-Bablok regression analysis, close correlation between methods (i.e. FACSCalibur versus Daktari prototype) was observed. For subjects with counts below 800 cells/mm^3, a coefficient of determination R^2=0.86 was found. Correlation became weaker for counts above 800 cells/mm^3. The Bland-Altman comparison demonstrated a bias of 17 cells/mm^3, and an imprecise limit of agreement range above 300 cells/mm^3. It should be mentioned, however, that variation around the mean drastically increased in the clinically irrelevant range of >800 cells/mm^3, which makes the LOA more acceptable for lower CD4 count ranges. For determining CD4 counts below 350 cells/mm^3, sensitivity and specificity were 0.90 and 0.97[82].

While these results are promising, it would be premature to assume they are conclusive. For one thing, many technical improvements have been made since this 2007 prototype, likely but not necessarily improving diagnostic accuracy. Also, the sample size was quite small, making the data findings mostly directional. Furthermore, the clinical setting of the Massachusetts General Hospital does not remotely compare to the type of resource-poor, rural settings in which Daktari CD4 tests are intended to be used. Caution must therefore be exercised when drawing conclusions from these initial findings.

Currently, a validation study is being conducted in Botswana, in which the conditions of the study will more closely adhere to the real Daktari CD4 device application. This particular study focuses on HIV positive pregnant women, and plans to recruit 80-90 subjects starting in

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[81] WHO. (2010) *Technical Brief on CD4 Technologies* [PDF file}. World Health Organization. Retrieved from www.who.int/diagnostics_laboratory

[82] Cheng X., *et al.* (2007) A microchip approach for practical lab-free CD4+ T-cell counting of HIV-infected subjects in resource-poor settings. *Journal of Acquired Immune Deficiency Syndromes (JAIDS), 45 (No 3),* pp. 257-261

January 2013. After subject recruitment, the validation study should last between 12 and 16 months. Accuracy, as measured by correlation coefficients, bias and LOA, and misclassification of pre-defined thresholds, is the primary endpoint of the study[83]. For the potential application of Daktari CD4 in the Mexican market, validation studies must also be performed in Mexico. The data obtained from all of these studies will further validate the current findings of diagnostics accuracy, as well as provide a stronger basis for the implementation of Daktari CD4 in Mexico.

Currently, no direct competitor of Daktari CD4 (i.e. Alere's PIMA or mBio's SnapCount) has conducted validation studies in Mexico. Nonetheless, Alere's PIMA has the commercial advantage, as it was the first among the three to conduct validation studies in Africa and Asia. The PIMA validation studies in Zimbabwe[84], Mozambique[85], and Thailand[86], for instance, show sensitivities and specificities in ranges above 0.90, and acceptable to imprecise LOAs.

For the purpose of illustrating the quality versus convenience tradeoff to be made with POC CD4 devices, the characteristics of a Daktari CD4 device are assumed. For instance, a sensitivity and specificity of 0.90 and 0.97 are assumed (threshold 350 cells/mm^3), as well as acceptable LOA and a high (>0.80) correlation coefficient. It is important to understand how this tradeoff affects the applicability of POC CD4 count diagnostics, and in which of the three segments of need the tradeoff is more or less relevant. For the remainder of this chapter 4, "Daktari CD4" will be used as a representative POC CD4 count device (like Alere's PIMA, mBio's SnapCount, and Daktari's Daktari CD4) that illustrates the type of tradeoffs that a public health official in Mexico would face.

For the first segment of need, that of off-site use during proactive campaigns, the convenience factor clearly outweighs any loss of diagnostic accuracy. In rural areas, where there is no access to flow cytometry, and samples would be costly and logistically burdensome

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[83] Botswana Harvard AIDS Institute. (2009). *Validation of a Portable Instrument of Point-of-Care CD4 Testing.* [PDF file].

[84] Mtapuri-Zinyowera S., *et al.* (2010). Evaluation of the PIMA point-of-care CD4 analyzer in VCT clinics in Zimbabwe. *Journal of Acquired Immune Deficiency Syndromes, 55,* pp. 1-7

[85] Jani I., *et al* (2011). Accurate CD4 T-cell enumeration and antiretroviral drug toxicity monitoring in primary healthcare clinics using point-of-care testing. *AIDS, 25,* pp. 807-812

[86] Sukapirom K., *et al.*(2011). Performance evaluation of Alere PIMA CD4 test for monitoring HIV-infected individuals in resource-constrained settings. *Journal of Acquired Immune Deficiency Syndromes, 58,* pp. 141-147

to transport, Daktari CD4 would be a successful diagnostic tool. The following scenario of initial care could be conceived: first, patients are diagnosed using HIV rapid tests, like Uni-gold. There is a 0.3% probability of an HIV-negative patient to be categorized as HIV-positive (specificity of 0.997), but HIV-positives do not test negative (sensitivity of 1.00)[87]. Fingerstick blood samples are taken from those who test positive, and within ~10 minutes a CD4 count is established using Daktari CD4. For the 0.3% of false positives there is an extremely low probability (less than 1 in 10,000) of an individual intrinsically having low CD4 counts that are not HIV related[88]. Therefore, the probability of a patient in a proactive campaign both testing positive in an HIV rapid test and having CD4 T cell depletion is less than three in a million. For all intents and purposes, all low count results (<500 cells/mm^3) who rapid tested HIV positive, are therefore true HIV positives. Nonetheless, there is a 10% chance for patients being misclassified below 350 cells/mm^3, and a 3% chance of a patient being misclassified above 350 cells/mm^3 (because of the assumed 0.90 sensitivity and 0.97 specificity). Taking this into account, **Figure 4-3** summarizes the resulting scenarios:

Figure 4-3: Scenario Comparison with and without Daktari CD4 in Off-site Campaign Use

Base of 1,000 HIV-positive patients
*Assumption: 50% of population with true below-threshold CD4 counts*

Scenario 1: with use of Daktari CD4

	True <350 cells/µl **ART needed**	True >350 cells/µl **ART NOT needed**	
Testing <350 cells/µl	A: 485 ART	B: 50 Premature ART	535
Testing >350 cells/µl	C: 15 Mistaken follow-up	D: 450 Follow-up	465
	500	500	1,000

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[87] Trinity Biotech (2012). Point of care products overview. Retrieved from http://www.unigoldhiv.com
[88] Centers for Disease Control and Prevention (CDC). (1992). Unexplained CD4+ T lymphocyte depletion in persons without evident HIV infection – United States. *Morbidity and Mortality Weekly Report (MMWR).* Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/00017329.htm
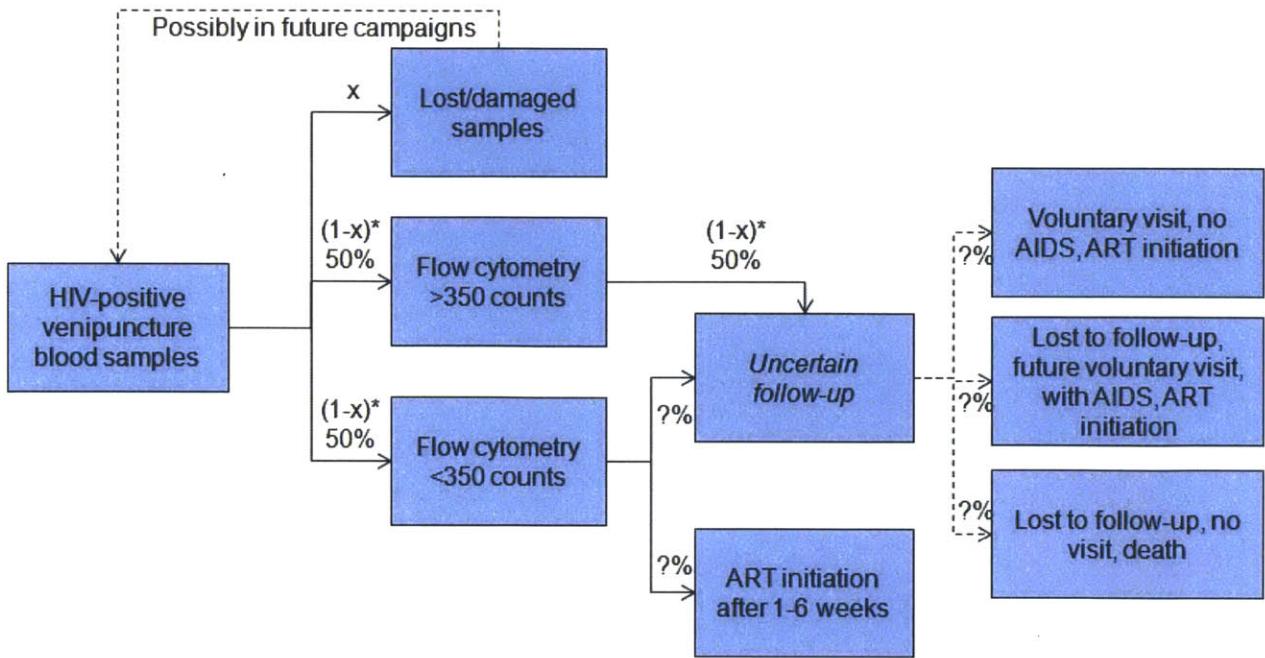
In **Figure 4-3**, scenario 1, the "A" group are true positives (i.e. true CD4 count <350 cells/µl, actually testing <350 cells/µl). Group "B" are false positives (i.e. true CD4 count >350 cells/µl, actually testing <350 cells/µl). Group "C" are false negatives (i.e. true CD4 count <350 cells/µl, actually testing >350 cells/µl). Finally, group "D" are true negatives (i.e. true CD4 count >350 cells/µl, actually testing >350 cells/µl). The following, summarizes the tradeoffs made for each segment of need.

A) A significant number (48.5%) of patients will be properly (and *immediately*) initiated in ART. Without POC tests, these patients would have otherwise received ART much later in the future or none at all, risking disease progression and the associated financial costs.

B) Some patients (5%) will receive premature ART, thus temporarily incurring unnecessary monetary expenses and treatment risks and side effects. Even with flow cytometry tests later showing true CD4 counts above 350 cells/µl, ART will not be interrupted, since there is real risk of developing drug resistance if therapy is interrupted[89]. This occurs because the virus' ability to replicate and mutate into drug-resistant mutations is inversely proportional to

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[89] Abbas A. K., Lichtman A. H., Pillai S. (2007). *Cellular and Molecular Immunology* (6th ed., pp. 476-487). Philadelphia, PA: Saunders

the level of drug pressure and the degree of viral suppression that is undergoing[90]. Therefore, drug resistance is a function of, among other factors, adherence to ART without interruptions[91,92]. The ART symptoms and adverse effects are numerous and varied. The more common and mild effects include "feeling sad", numbness in hands/feet, nausea, pain and lack of energy. In fact there are more that 15 mild symptoms and adverse effects that at least one third of HIV patients receiving ART experience[93]. Other less common but more serious adverse effects include anemia, peripheral neuropathy, retinoid toxicity, and hypersensitivity reactions. These are usually treated along side ART, without interrupting ART. Other, more subtle but equally serious adverse effects include lactic acidosis, bleeding disorders, and hepatotoxicity, among others[94]. In fact, hepatotoxicity and ART-associated drug-induced liver injury occurs in 9 to 30% of patients receiving ART, depending on the ART regimen[95]. Therefore, initiating ART prematurely in this group of patients makes them prone to developing, for instance, hepatotoxicity more rapidly. Without Daktari CD4, these patients would have eventually reached immunosuppresion, so these costs and risks are only temporary (1-24 month range). These patients would have otherwise continued with their lives until a future hypothetical voluntary visit.

C) Other patients (1.5%) will not receive ART, when they actually need it. This is an undesirable outcome, since these patients are at a high risk of rapidly progressing into AIDS. Without Daktari CD4, these patients would have faced the same outcome, unless they were planning on making a voluntary visit in the immediate future and were dissuaded by the POC results. Nonetheless, if patients were observed to have AIDS-associated symptoms it is likely that even without the low POC CD4 counts that they would be initiated in ART.

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[90] Bangsberg D., Kroetz D., Deeks S. (2007). Adherence-resistance relationships to combination HIV antiretroviral therapy. *Antiretroviral Therapies – Current HIV/AIDS Reports, 4,* pp 65-72

[91] *Ibid.*

[92] Shapiro J. (2005). The latest advances against ART drug resistance. *Medscape HIV/AIDS, 11 (No 2)*

[93] Farranct L., *et al.* (2012). The prevalence and burden of pain and other symptoms among South Africans attending HAART clinics. *South African Medical Journal (SAMJ), 102 (No 6),* pp. 499-500

[94] Montessori V., *et al* (2004). Adverse effects of antiretroviral therapy for HIV infection. *Canadian Medical Association Journal (CMAJ), 170 (No 2),* pp. 229-238

[95] Schutz C., *et al.* (2012). Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa. *South African Medical Journal (SAMJ), 102 (No 6),* pp. 506-511

D) Finally, a significant number of patients (45%) will be in follow-up, thus encouraged to schedule visits to CAPASITS in the near future (every four months).

As a public health official in Mexico, the decision to use POC CD4 count diagnostics in this first segment of need becomes relatively straightforward. In the absence of diagnostic and treatment alternatives for this segment of off-site campaigns, the use of POC CD4 diagnostics is easily justified. As previously stated, the majority of interviewees (27 out of 28) supported the use of POC CD4 count diagnostics in this segment of need. These are patients that the Mexican health care system would like to be serving via the CAPASITS voluntary visit, but these visits are not occurring. Therefore, if a mechanism can be found, at or below the incremental cost of current flow cytometer CD4 counts, to immediately assess CD4 counts at the patient POC, then public health officials would approve and encourage the use of POC CD4 counts for this segment of need. Even more so, with a POC CD4 count device (like Daktari CD4), off-site rural campaigns may significantly increase (as expressed by 23 out of the 28 interviewees), and even become a major important avenue for identifying and diagnosing those HIV/AIDS patients currently unidentified and undiagnosed.

For the second segment of need, that of initial CD4 count during a voluntary visit to CAPASITS before initiating ART, the convenience factor is a decision aid for starting patients with ART, especially helping in those cases where ART is required immediately. A complement scenario (and not a substitute scenario) is assumed for this second segment of need. That is, POC CD4 counts are tested for all visiting patients, while still taking venipuncture samples and sending them to a laboratory. Furthermore, a "border line" range would be used (for instance, CD4 counts between 300 and 400 cells/mm^3). While there is no supporting data for the breakdowns of where the diagnostic tests will land (i.e. below the "borderline" range, within, or above), a few simple assumptions can be made to illustrate what the diagnostic picture could look like. Firstly, one can assume a range of true CD4 counts between 0 and 700 cells/mm^3. Also, one can assume that true positives (the "A" group in **Figure 4-3**) are equally and linearly distributed from count 0 to count 350 cells/mm^3. One can also make similar assumptions for false positives ("B" group in **Figure 4-3**), false negatives ("C" group in **Figure 4-3**), and true

negatives ("D" group in **Figure 4-3**). After applying these simple assumptions, and adding a "borderline" range of measurement, **Figure 4-4** illustrates the resulting scenarios:

Figure 4-4: Scenario with Daktari CD4 in Initial CD4 Count at CAPASITS Voluntary Visit

Base of 1,000 HIV-positive patients
Assumption: 50% of population with true below-threshold CD4 counts

	True <350 cells/µl **ART needed**	True >350 cells/µl **ART NOT needed**	
Testing <300 cells/µl	A: 415 ART	B: 43 Premature ART	458
Testing between 300 and 400 cells/µl	C: 74 "borderline"	C: 72 "borderline"	146
Testing >400 cells/µl	D: 11 Mistaken follow-up	E: 385 Follow-up	396
	500	500	1,000

A normal distribution of false positives, false negatives, true positives, and true negatives, across their respective ranges, would likely have been a more accurate representation of what a diagnostic picture would look like. More importantly, such a normal distribution scenario would have yielded significantly *less* false positives and false negatives (i.e. premature ART and mistaken follow-ups), and *less* true positives and true negatives, clustering all of these groups closer into the "borderline" "C" group. Nonetheless, **Figure 4-4** serves its purpose of illustrating a "conservative" diagnostic picture, which looks as follows:

A) A significant portion of patients (41.5%) will initiate ART immediately upon their visit. Without Daktari CD4, a small number of these patients (estimation suggest ~10%) would not return to their next appointment due to attrition (either never return, or delay ART until clearer AIDS-associated symptoms appear), while most would initiate ART but perhaps 1-2 months later, risking disease progression.

B) Some patients (4.3%) will start premature ART. These patients will simply continue ART indefinitely as a means of controlling their disease. Without Daktari CD4, these patients would have been followed-up until their CD4 counts decreased further, so as to have a timely initiation of ART.

C) Another group of patients (14.6%) will fall under the "borderline" group, with CD4 counts between 300 and 400 cells/mm^3. For these patients, flow cytometer CD4 counts will confirm whether they require ART or not. Without Daktari CD4, these patients' course of action would be exactly the same in that they will wait for flow cytometer results before making a decision regarding their course of action. In this borderline group, there are incremental costs, but no health gain.

D) A small group of patients (1.1%) with low CD4 counts will not initiate ART immediately, even though they need it (unless, of course, their clinical picture is very poor, in which case the CD4 count is secondary measure). These patients will still have their flow cytometry CD4 counts, and initiate ART (after attrition) 1-2 months later. Without Daktari CD4, these patients' course of action would be exactly the same in that they will wait for flow cytometer results before making a decision regarding their course of action. In this group as well, there are incremental costs, but no particular health gains.

E) Finally, a significant number of patients will continue in follow-up, just as they would have if their CD4 counts had not been determined with Daktari CD4.

In short, the use of POC CD4 count device like Daktari CD4 in the second segment of need would: accelerate initiation of ART in at least 80% of patients who imminently need it, while making at most 8% of patients who do not yet need ART begin their regimens prematurely.

As a public health official in Mexico, the decision to implement POC CD4 count diagnostics in this segment of need is not as straightforward as it is for off-site campaigns. This decision requires the weighing of "costs" and "benefits" (both health and economic related), and deciding whether the equation yields a net "positive" or negative" result. On one side, the primary benefit of using Daktari CD4 is a better health outcome for 485 patients (out of 1,000), along with the potentially saved costs of lower transmission and fewer clinical events. The

primary costs are: i) premature ART and incurring the associated adverse effects for some patients (43), and ii) incurring the cost of ~3 POC CD4 counts per year for all 1,000 patients. The costs of these tests (as will be discussed in the next chapter) range in the US$8-20 per POC CD4 count test, which yields an incremental US$24-60 per patient per year. Just to put these numbers in perspective, current ART regimens in Mexico cost between US$1,000 and US$3,000 per patient per month, yielding an annual cost of US$12,000-36,000 per patient[96].

Once again, the role of this section is not to conduct cost-effectiveness analyses, but rather to illustrate the types of tradeoff that a health official would make when using POC CD4 count diagnostics. Given these illustrations and relative costs, as previously stated, the majority of interviewees (24 out of 28) viewed possible the use of POC CD4 counts in this segment of need, while 20 out of 28 viewed it as probable. Therefore, it appears that the "costs" versus "benefits" equation (both economic and health) yields a positive result in the minds of those closest to the policy and treatment of this segment of need in Mexico.

For the third and final segment of need, that of follow-up CD4 measurements after ART has already been initiated, the value proposition is purely economic. For patients already in ART, both viral load and CD4 counts are measured every four months, according to treatment guidelines. In the absence of viral load measurements, CD4 counts are instrumental in assessing efficacy of a given ART. But when VLs are measured, CD4 counts are usually not even considered. The undetectability of viral copies is the primary diagnostic finding determining success of ART[97]; that, and clinical progression, of course. Nonetheless, CD4 counts are commonly taken and updated in the patient's medical history. Therefore, a less specific and sensitive CD4 count at this stage would effectively not harm the disease management and treatment. Consequently, if the CAPASITS can save a reasonable percentage of the costs associated with flow cytometry CD4 count tests, and they can do so without affecting patients' well being, they may very well use a POC CD4 count diagnostic like Daktari CD4.

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[96] Córdoba Villalobos J. A., Hernández Ávila M., Izazola Licea J. A., Magis Rodríguez C., García de León C., Hernández Tepichín G. (2009). *El VIH/SIDA en México 2009.* CENSIDA, Secretaría de Salud. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html
[97] CENSIDA, Secretaría de Salud. (2012). *Lineamientos para el tratamiento antirretroviral de personas con VIH para instituciones del sistema nacional de salud* [PDF file]. Retrieved from http://www.censida.salud.gob.mx/

As previously discussed, most of the relevant interviewees (8 out of 9) expressed they would consider using a POC CD4 count, like Daktari CD4, instead of flow cytometry CD4 count test for the follow-up counts after the patient has initiated ART. The cost per CD4 count test (as will be discussed in the next chapter) ranges in the US$8-20 per test with a POC CD4 count device like Daktari CD4, versus a US$45-65 per test with a standard flow cytometry test.

Figure 4-5 summarizes the treatment avenues, relative magnitudes, and identified segments of need previously discussed.

Figure 4-5: Segmentation of HIV/AIDS Patients in Mexico According to Treatment Avenue and Segment of Need[98,99,100]

Number of HIV/AIDS Patients in Mexico
Thousands of patients, 2010
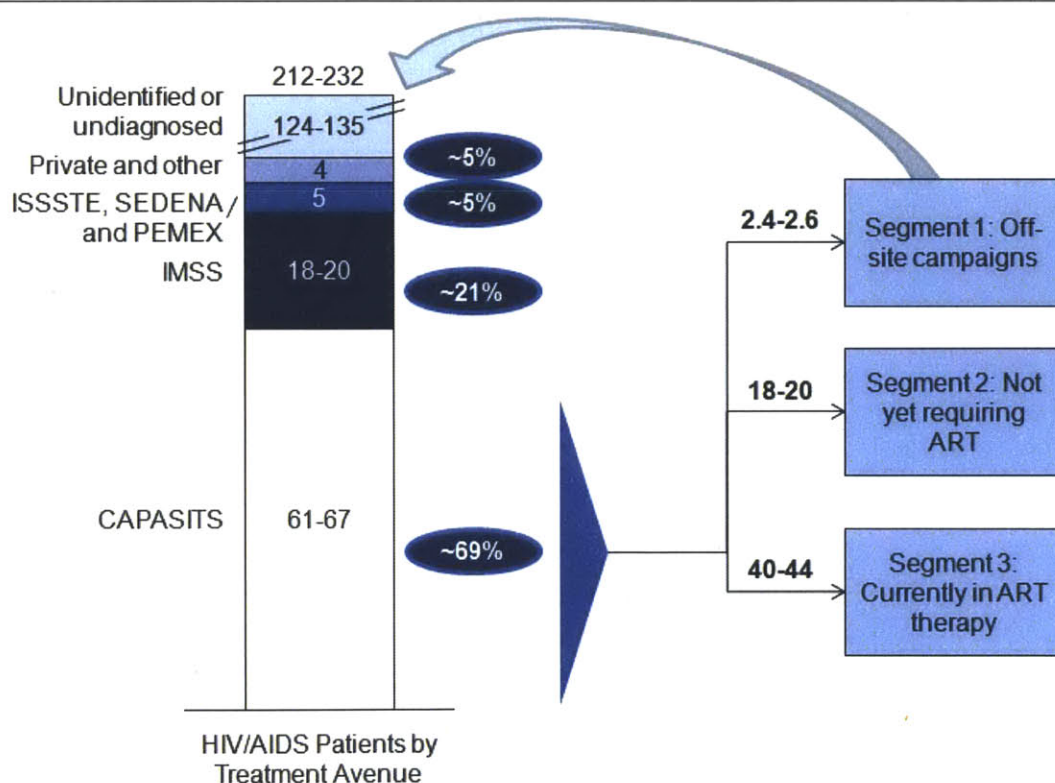
[98] Instituto Nacional de Salud Pública. (2009). *25 años de SIDA en México. Logros, desaciertos y retos* (2nd ed.), pp. 101-120, and 303-314. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html
[99] Izazola Licea J. A., Sucilla Pérez H. (2011). *Panorama epidemiológico del VIH/SIDA en México* [PDF file], CENSIDA, Secretaría de Salud, 1er Congreso Internacional en VIH e ITS, Monterrey, México
[100] Córdoba Villalobos J. A., Hernández Ávila M., Izazola Licea J. A., Magis Rodríguez C., García de León C., Hernández Tepichín G. (2009). *El VIH/SIDA en México 2009.* CENSIDA, Secretaría de Salud. Retrieved from http://www.censida.salud.gob.mx/interior/panorama.html

Chapter 5: Primary Hypothesis #2: Relevant Market Potential and Adequate Commercial Viability

Market Size Estimations

Estimating the market size for POC CD4 counts in Mexico is a function of both the identified medical needs from Chapter 4, and of the sensitivities such segment sizes may have with other POC CD4 market factors. The following section briefly outlines these market sensitivity factors at play, and uses the conducted field interviews to preliminarily evaluate the likelihood of these factors shaping the size of the market for POC CD4 count devices.

As a baseline (from **Figure 4-5)**, the number of patients in the first segment of need, off-site proactive campaigns, is ~2,500 HIV/AIDS patients. The number of patients in the second segment of need, CAPASITS patients not yet requiring ART, is between 18,000 and 20,000. And the number of patients in the third segment of need, follow-up CD4 counts for patients currently receiving ART, is between 40,000 and 44,000.

Of these, the least certain of the estimations is that of off-site campaigns, as it is mainly based on interview declarations, and on extrapolations from observations at visited CAPASITS. Estimations regarding the second and third segment of need are commonly followed and published (see **Figure 4-5** sources) in Mexico on a yearly basis; they have become fairly standard and accurate, as they are based on the national HIV/AIDS patient IT system SALVAR that reports and manages all HIV/AIDS patients in the CAPASITS network.

These estimations yield a total target population of 60,400 to 68,600 patients. The optimal number of CD4 count tests per year, according to CENSIDA guidelines, is three (i.e. every four months). Nonetheless, there is no perfect adherence to the number of visits per year, and in reality it averages to 1.67 visits per year[101], yielding an estimated total CD4 count target market between 100,000 and 115,000 tests per year. According to undisclosed industry executives' market size estimations, the number of viral load tests performed through CAPASITS is in the order of 90,000 to 100,000 tests per year. The number of viral load tests

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[101] Izazola Licea J. A., Sucilla Pérez H. (2011). *Panorama epidemiológico del VIH/SIDA en México* [PDF file], CENSIDA, Secretaría de Salud, 1er Congreso Internacional en VIH e ITS, Monterrey, México

performed in a given year is usually very close to the number of CD4 count tests performed per year, since both tests are commonly ordered together. Obtaining market size estimations very closely matching the third party viral load estimates is an additional confirmation that the real number of CD4 count tests, through CAPASITS, is close to the stated numbers.

Starting from the number of 100,000-115,000 CD4 count tests per year, this baseline market size is divided into its components and analyzed for each segment's potential and sensitivities.

The first segment of need, off-site proactive campaigns, presently represents less than 5% of the current target market for CD4 counts tests. While 4,000-4,300 CD4 count tests per year makes this segment of need the smallest among all three, this segment has the highest potential to grow further and become a more relevant source of CD4 count tests. Using the interviews as the main sources of inference, two key factors were found to influence the potential growth of this segment of need.

On the one hand, the belief of whether or not decentralized healthcare models represent a viable answer to public health concerns (like identifying undiagnosed HIV/AIDS patients) is at the center of expanding or not this segment of need. Whether or not decision makers believe that conducting off-site proactive campaigns in suburban and rural areas of Mexico is a valid approach to a healthcare situation, be it in the HIV/AIDS landscape or not, will directly influence the resources and efforts put behind CAPASITS-associated off-site campaigns. While only a few interviewees (2 out of 40) viewed centralized models as the avenue improving care for those undiagnosed and unidentified HIV/AIDS patients, the overwhelming majority (37 out of 40; 1 did not comment on this topic) saw decentralized healthcare models as a primary avenue for generating impact and identifying new HIV/AIDS in Mexico.

On the other hand, the more the Seguro Popular umbrella continues to affiliate and cover the population that is currently uninsured, it was identified, the more likely it is for off-site campaigns to have greater popularity and acceptance among the target population of HIV/AIDS patients. Among CENSIDA, CAPASITS, Secretary of Health, and individual patient interviews, it was collectively stated that being insured under Seguro Popular increased the patients' likelihood of being informed about future off-site campaigns in their regions. Also, this

increased their confidence that they would be eligible for coverage under such campaigns (even though eligibility for HIV/AIDS treatment through CAPASITS is universal for anyone outside the social security system). From Seguro Popular's precedent of rapidly increasing coverage of uninsured populations in the past years[102], it is expected that this factor plays a role in strengthening off-site campaigns for identifying HIV/AIDS patients and increasing the number of CD4 count tests.

Stating a specific number of additional CD4 count tests in this segment of need, given the previously mentioned factors that may influence the growth of this segment, would be speculative. Nonetheless, interviewees were asked about the growth potential of this segment (particularly those closest to off-site campaign decision making like CENSIDA, CAPASITS, and the Secretaries of Health). It was identified as highly likely that off-site campaigns increase their reach by 2x-5x of what they currently serve, as medium likelihood to unlikely that they increase their reach by 6x-10x, and as very unlikely that they increase their reach more that 10x their current reach.

Figure 5-1 summarizes the baseline and potential CD4 count tests sizes, along with the different factors that may affect the potential for this segment of need.

Figure 5-1: Baseline and Potential Markets for the First Segment of Need: Off-site Campaigns
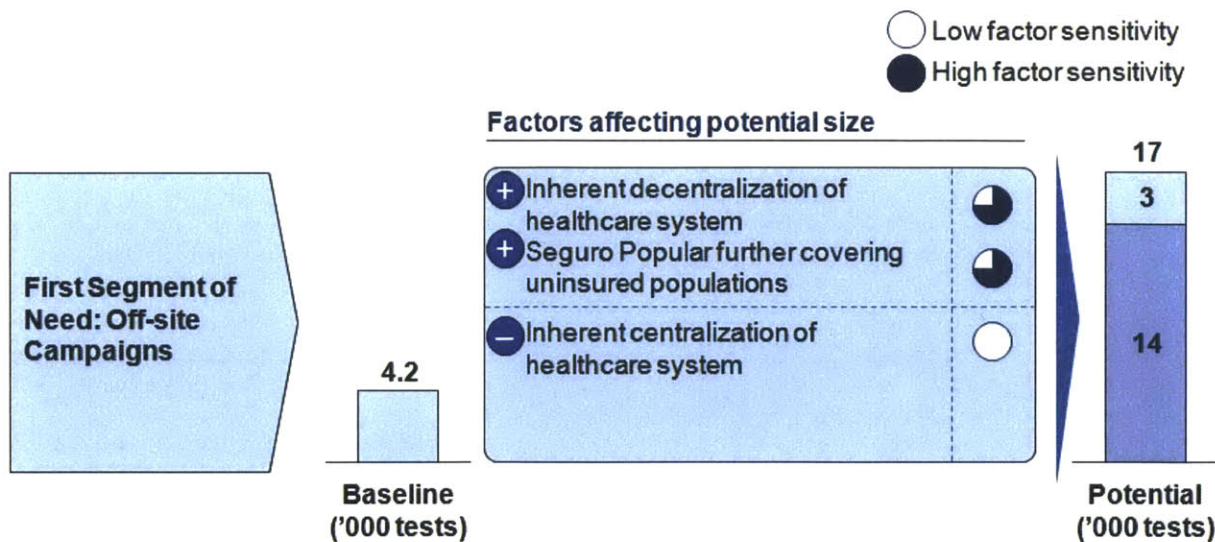
[102] Chertorivski-Woldenberg S. (2011). Seguro Popular: logros y perspectivas. *Gaceta Médica de México, 147,* 487-496

The second segment of need, CD4 count test at CAPASITS before ART is initiated, represents ~30% of the target patient population (18,000 to 20,000 patients). This segment yields some 30,000 to 33,000 CD4 count tests per year. While several factors might presumably influence the potential size of this segment of need (see **Figure 5-2**), the primary factor identified is that of patient adherence to CD4 count control visits. Increasing the number of control visits for CD4 counts to the recommended three per year, which is currently identified as a priority within CENSIDA and CAPASITS[103], would increase the number of CD4 count tests done per year to 54,000 to 60,000 CD4 count tests per year. While raising CD4 count adherence is a priority, it would be unrealistic to expect perfect adherence. Therefore, for this second segment of need, the defined potential should be better interpreted as an upper bound of opportunity.

Figure 5-2: Baseline and Potential Markets for the Second Segment of Need: CD4 Counts during CAPASITS Visits before ART is Initiated
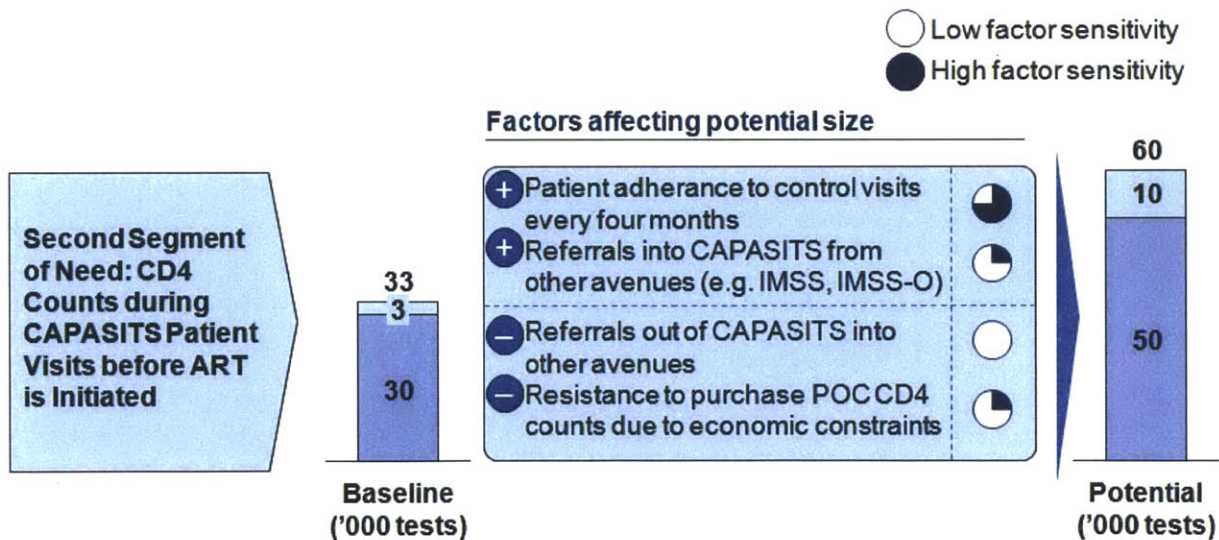
The third segment of need, control CD4 count measurement after ART is initiated, represents the largest portion of target patients, with 40,000 to 44,000 patients in total, yielding between 67,000 and 73,000 CD4 count tests per year. However, this segment has the

[103] CENSIDA, Secretaría de Salud. (2012). *Lineamientos para el tratamiento antirretroviral de personas con VIH para instituciones del sistema nacional de salud* [PDF file]. Retrieved from http://www.censida.salud.gob.mx/

least potential to grow, and a relevant risk of not converting into POC CD4 counts from traditional flow cytometry. Physicians and direct users of CD4 count tests expressed high likelihood of accepting POC CD4 counts instead of the standard flow cytometry tests, as control tests for follow-up patients that already initiated ART. Furthermore, among CENSIDA, CAPASITS, and State Secretary of Health there was enthusiasm around the potential monetary saving if such substitution occurs. Nonetheless, serving this segment of need implies competing directly against flow cytometer companies like Becton Dickinson and Beckman Coulter, as opposed to complementing their offering. Competitively speaking (as will be later discussed), this is a more hostile environment for any POC CD4 diagnostic device company, like Daktari, to enter.

Figure 5-3: Baseline and Potential Markets for the Third Segment of Need: Control CD4 Counts for CAPASITS Patients after ART is Initiated
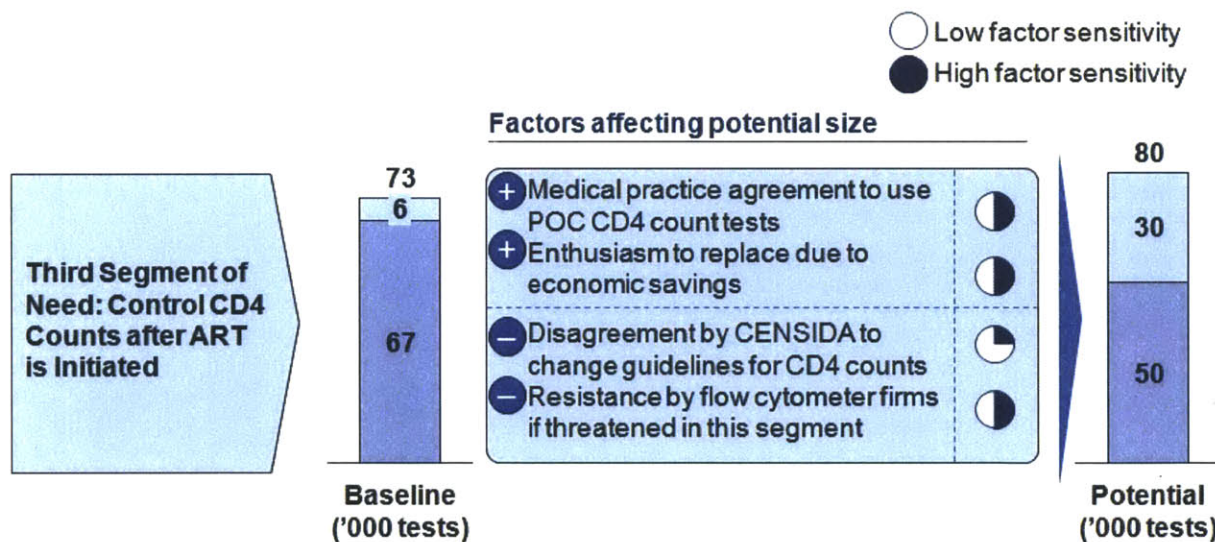
All together, these three segments of need represent a baseline of ~110 thousand CD4 count tests per year; a baseline that may grow to a potential of roughly twice its size (~197 thousand CD4 count tests per year). This estimated market size positions the opportunity in Mexico as a moderate to small one, although highly concentrated in a few locations (the CAPASITS). The typical scenario of a sub-Saharan opportunity is that of a couple of multiples of

this Mexico's opportunity, but significantly more spread in terms of point of care[104]. **Figure 5-4** summarizes the baseline yearly CD4 counts, and their growth potential.

Figure 5-4: Total Baseline and Potential CD4 Count Tests per Year in Mexico:

Baseline and Potential of CD4 count tests per year in Mexico
Thousands of tests
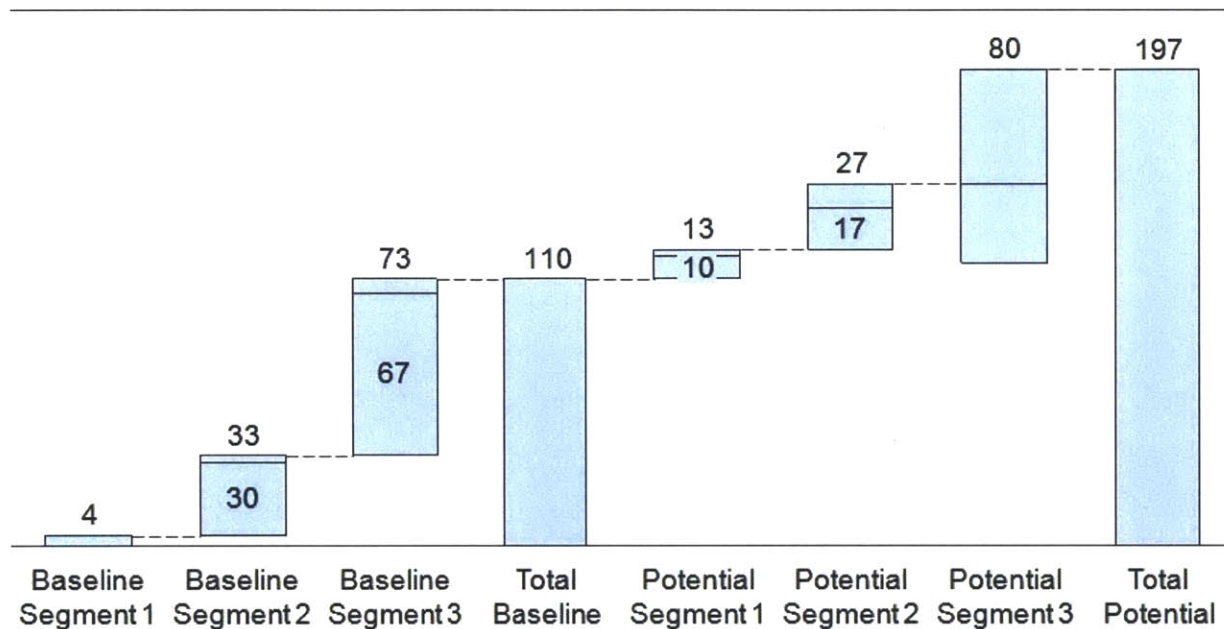
All of this is to say that, from a high-level market perspective, the opportunity in Mexico is relevant but not enormous. Assuming a price per CD4 count of $10-$20 per test, the opportunity size is in the US$1 Million to US$4 Million per year, excluding sales of devices. For small start-up companies of the like of Daktari and mBio, these numbers are relatively attractive. For established incumbents, like Beckton Dickinson and Beckman Coulter, who have multiple divisions and product lines, these market sizes are commonly of second priority.

So far, the discussion has revolved around the baseline and potential numbers of CD4 count tests performed (e.g. Daktari CD4 cartridges that could be sold). However, there is also the question of how many Daktari CD4 devices are needed in order to operate this number of CD4 count tests per year (see **Figure 2-5** from Background chapter). There are at least two ways to estimate this number. One approach takes into account device throughput, while the other

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[104] Chen G., Lo B., Patel VJ., Sayed L. (2010). Market Entry Strategy for Uganda. [PDF File]. *Daktari's internal documents.*

approach is a more straightforward estimation based on Points-of-Care where the device is needed (mainly the CAPASITS).

CD4 count tests using POC CD4 count devices take between 10 minutes and 25 minutes. Daktari in particular, takes between 10 and 15 minutes between sample taken and cartridge disposed after obtaining results. Therefore, Daktari's throughput is ~4 samples per hour, of ~16 samples per 4-hour day (usually, samples are taken in the morning). This yields, assuming 5 days a week, and 52 weeks a year, some ~4,160 per year, at full capacity. Considering that keeping a device at full capacity is very difficult, a more conservative throughput range of 2,000 to 4,000 tests per year would be more appropriate, averaging at ~3,000 tests per year. Given the number of tests to perform, between ~110,000 and ~200,000, at least 36 to 68 devices would be needed in order to process the estimated baseline and potential test volume. This is the lower end estimation of the required number of devices simultaneously working at any given time.

A more straightforward estimation approach looks at the number of CAPASITS in Mexico, 70, and assumes that every CAPASITS must have at least one device on-site in order to provide the coverage needed to serve the CD4 count test demand. A few outlier CAPASITS receive higher patient volume than the standard CAPASITS. These are primarily the ones located in Mexico City, Mexico State and Monterrey. For these CAPASITS, the number of devices needed to satisfy their demand could be as many as three per CAPASITS. Taking into account these higher-volume CAPASITS, the number of devices would be closer to 80 rather than 70.

Additional devices would also be needed to conduct off-site, proactive campaigns, so as to not occupy the devices already on-site. For off-site campaign purposes, either every state (32 of them) has an additional CD4 count device, or instead every CAPASITS (70) has an additional CD4 count device.

These two approaches yield a lower bound of 36 to 68 devices, and an upper bound of 80-150 CD4 count devices in total. As will soon be discussed, maximizing the number of sold devices (by Daktari or by its competitors) is not necessarily a core interest, as it is very common for diagnostics companies to provide their devices free of cost, but embed the cost of the

device in the price charged per unit test (with such prices varying according to volume). Therefore, as long as there are enough devices in place to manage the volume of CD4 count tests, maximizing the sale of devices is not necessarily a priority.

Current Competitive Forces

Figure 5-5: Competitor profiles[105]

	BD FACSCalibur	PointCare	Pima	Daktari
Price (device)	$30k-$60k	$15k-$20k	$29k	$1k-$2k
Price per test	$7-$10 $30-$50 (Mex)	$10-15	$5-$7	$5-$10
Assay time	4 mins	8 mins	20 mins	8 mins
Battery life	No option	6 hours	6 hours	2-3 days
Relative (%) CD4	Yes	Yes	No	No

Figure 5-5 summarizes the relative characteristics of the representative Daktari competitors. In order to analyze potential competitive dynamics that Daktari may face, it is important to separate the discussion into i) competitive forces vis-à-vis flow cytometers, and ii) competitive forces vis-à-vis other POC CD4 count devices.

First, relative to flow cytometers (like FACSCalibur on **Figure 5-5**), Daktari CD4 has the advantage of a significantly cheaper device (~$1,500 versus ~$40,000), and a much lower price per test in Mexico ($5-$10 versus $30-$50 per test), while sacrificing little in terms of throughput. Agreements between flow cytometer companies and State Laboratories (or other hospital laboratories for that matter) usually present a range of price per test options, depending on the purchase mechanism that is used. An outright purchase of the flow cytometer comes with a lower price per test (in Mexico, usually in the ~$30 per test range). However, the most common "purchase" mechanism is that in which the flow cytometer device is provided to the laboratory, free of charge, but the price per test is raised. Depending on the

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[105] Chen G., Lo B., Patel VJ., Sayed L. (2010). Market Entry Strategy for Uganda. [PDF File]. *Daktari's internal documents.*

expected volume of tests, the price can oscillate between ~$40 per test and ~$50 per test, the lower price of course corresponding to higher volumes.

Expectedly, a Daktari CD4 price point per test that is anything between $5 and $10 would be of attractive value relative to flow cytometers from a purely economic perspective (that is, on top of the ability to serve some of the POC segments of need outlined in the previous chapter). Notice also that a $1 incremental price charged per test would recover the cost of the device as quickly as in 6 months for a device working at a ~3,000 tests per year throughput. At this stage, it becomes clear why POC CD4 counts for the third segment of need (that of control CD4 counts after ART has initiated) could replace flow cytometer measurements.

It also becomes apparent why flow cytometer device companies, like Becton Dickinson and Beckman Coulter would become resistant to POC devices entering the third segment of need. In the first and second segments of need, POC CD4 counts either serve currently unmet markets or complement the present offerings in an existing market in order to enhance patient outcome. In contrast, this third segment of need in question implies competing head to head against incumbent flow cytometry companies. Flow cytometer companies will likely react aggressively if they feel threatened by POC CD4 count device companies. As implied by **Figure 5-5**, flow cytometer companies like BD and BC have the ability to decrease their price per test significantly, especially when compared to their current Mexican offering of price per test. In many other countries, including sub-Saharan countries, flow cytometer price per tests can be as low as $7-$10 per test, which brings them to the same price level per test of other POC CD4 count diagnostics like Daktari CD4. It is unclear whether these lower prices are only available when bundled to the purchase of the device; understanding such cases would elucidate on their flexibility to decrease prices in Mexico. Furthermore, knowing the marginal costs of the flow cytometers themselves, would also aid in forecasting the price reactions that these companies might have. Not only have the Becton Dickinsons and Beckman Coulters of the world demonstrated in other markets that their pricing can be more competitive, but they also have the financial muscle to undergo a price war for a much longer time span than the POC CD4 count device companies might.

In short, it is important to realize that the highest resistance from incumbent flow cytometry companies will be observed in the third segment of need, and that the dynamics played out in this segment will strongly depend on the market entry choices made by Daktari (or by other POC CD4 count companies) to approach each of the segments of need.

Second, relative to other POC CD4 count diagnostics, Daktari is in a very strong position, considering the factors of price per test, price of equipment, battery life, and throughput. Daktari's manufacturing projections, the details of which will remain undisclosed, estimate that a price range between $5 and $10 per test would provide a "healthy margin" to sufficiently cover direct and indirect costs. Furthermore, Daktari's technology makes it a system of very low power consumption, as demonstrated by its extended battery life. This characteristic certainly becomes attractive, especially for off-site campaigns. Throughput, furthermore, is in the high range, as it is almost three times as fast in processing samples as Alere's PIMA. While information regarding marginal costs of equipments has been elusive, the significant differences in price point positioning suggests but does not confirm that Daktari has greater flexibility to price its devices and therefore to receive greater margins.

Another major factor, that is still uncertain, is how diagnostic accuracy will compare across the different POC CD4 count platforms. So far, Alere's PIMA validation study results place their platform device in acceptable LOAs, and sensitivities and specificities above 0.90[106,107,108], making it comparable to what Daktari CD4 promises to offer in terms of diagnostic accuracy. mBio has yet to show validation study evidence to support its comparable claim of diagnostic accuracy. The development of validation studies by all of these CD4 count companies, and the relative diagnostic accuracy positioning of each will certainly play a role in their ability to capture the opportunity presented in the Mexican market.

Equipment reliability will also play a significant role in the battle between different POC CD4 count devices. PointCare, being a single flow platform using complex optical and flow

[106] Mtapuri-Zinyowera S., *et al.* (2010). Evaluation of the PIMA point-of-care CD4 analyzer in VCT clinics in Zimbabwe. *Journal of Acquired Immune Deficiency Syndromes, 55,* pp. 1-7
[107] Jani I., *et al* (2011). Accurate CD4 T-cell enumeration and antiretroviral drug toxicity monitoring in primary healthcare clinics using point-of-care testing. *AIDS, 25,* pp. 807-812
[108] Sukapirom K., *et al.*(2011). Performance evaluation of Alere PIMA CD4 test for monitoring HIV-infected individuals in resource-constrained settings. *Journal of Acquired Immune Deficiency Syndromes, 58,* pp.141-147

systems similar to those of standard flow cytometers, is likely to have the most problems with reliability. Alere, PIMA, and Daktari, on the other hand, all use technologies different in principle from flow cytometry. While they all promise more robustness, durability and reliability from a technological standpoint[109], it is yet to be confirmed in practice. This equipment reliability (or lack thereof) can also be supported by strong technical and service presence by the manufacturer. Both Becton Dickinson and Beckman Coulter have established good service practices in Mexico, according to State Laboratory interviews. It is yet to be determined what the strategies and competencies of the competing POC CD4 count diagnostics will be in terms of technical service and ability.

An equally relevant factor in the competitive landscape in Mexico, is how quickly each POC CD4 count device company enters the market, or if it enters the market at all. In this respect, Alere's PIMA has the advantage as it has established a commercial presence in sub-Saharan Africa, and is already starting to enter Latin America on a validation study basis. While Alere has no presence yet in Mexico, it has initiated validation study processes in Hiati, Jamaica, and Brazil[110]. It is likely that Alere will be the first POC CD4 count device company to enter Mexico, judging from its jumpstart in most other target countries.

Even more relevant to how quickly a company establishes a presence in the country, are the regulatory and market strategy choices made before that presence is even established. As will be briefly discussed in the following section, the choices of market positioning, regulatory navigation, and competitive battles will possibly be stronger determinants of success than the first comer advantage.

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[109] Boyle D. S., Hawkins K. R., Steele M. S., Singhal M., Cheng X. (2012). Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends in Biotechnology, 30 (No 1)*, pp. 45-54

[110] Alere (2012). About Alere – Investor Relations Retrieved from http://www.alere.com/EN_US/about-alere/investor-relations/press-releases/

Avoiding Pitfalls, and Recommended Positioning

One of the major challenges faced by POC CD4 count device companies entering Latin America is the question of how to approach the regulatory process.

Given that the need for POC CD4 counts in sub-Saharan Africa is alarming, there is much awareness, and plenty of advocacy voices, around POC CD4 count diagnostics. This helps regulators in these countries more clearly understand the needs of their populations, and the different tradeoffs that such CD4 count devices offer. The "quality" versus "convenience" tradeoff is top-of-mind among healthcare officials. As such, approvals of POC diagnostics, especially when targeted at diseases of major importance like HIV/AIDS, are treated differently than the gold standard technologies[111].

This is not usually the case for Latin American countries. The "quality" versus "convenience" tradeoff is not generally identified, particularly for HIV/AIDS. In Mexico there is no precedent for POC CD4 count diagnostics. Therefore, POC CD4 count device companies run the risk of being directly compared to flow cytometer CD4 count devices, which certainly have greater diagnostic accuracy standards. From the outside, it may seem tempting to undergo a regulatory process that directly compares POC CD4 count devices as or "non-inferior" to flow cytometers, since that would allow for entering and competing at every laboratory in the country. However, the level of diagnostic accuracy required for such an approval path has to be much higher than what validation studies are showing[112]. Therefore, the probability of approval under this paradigm is very low. If, however, flow cytometers and POC CD4 count devices are not compared head to head during their approval and regulatory processes, and are evaluated under separate diagnostic categories, the likelihood of approval would increase significantly.

To this point of approval and regulatory processes, interviews conducted confirmed this duality of interpretation and approaches. While a significant number of interviewees (15 out of 34; patients excluded) expressed either little knowledge or an undecided mindset on how to approach the regulatory process if they were the entering POC CD4 count company. Of the

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[111] Zachariah R., *et al.* (2011). Why do we need a point-of-care CD4 test for low-income countries? *Tropical Medicine and International Health, 16 (No 1),* pp. 37-41

[112] Chacon J., Diaz R., Murillo, personal communication, July 2012

remainder interviewees, 7 suggested an approach of positioning the POC CD4 count device as comparable/non-inferior to flow cytometers, while 12 suggested treating their approval and regulatory processes in a separate category from that of flow cytometers. These interview findings essentially confirm, I would argue, the lack of awareness of the "quality" versus "convenience" tradeoff that the POC CD4 diagnostics embody, and the type of benefits and improvements that they bring to a healthcare system. The initial steps taken in the approval and regulatory processes will predetermine the likely success or failure of entering POC CD4 count device companies.

Parallel to a regulatory strategy is the commercial positioning. For each of the three identified segments of need, the perceived role of a POC CD4 count device like Daktari CD4 is different. In the first segment of need (off-site campaigns), a Daktari CD4 would offer a solution to a need for which there is currently no other alternative; a very similar case to that of sub-Saharan countries and resource-limited regions. In the second segment of need (CD4 counts at CAPASITS before ART initiated), a Daktari CD4 would complement a healthcare service, thus improving patient outcome and reducing patient attrition. In the third segment of need (control CD4 counts after ART is initiated), a Daktari CD4 would replace the standard of care flow cytometer with a "cheap, good enough" alternative, because the medical practice would allow for it, and because there are economic savings to obtain.

Just as the need satisfied in each of the three segments is different, the commercial strategy, and therefore the message voiced to the customer, is also different. This brings me to ask two related questions: i) whether more than one message or commercial strategy should be used in order to capture the opportunity, and ii) if only one commercial strategy were to be used, which one should it be? In other words, should the market positioning being used in low-income sub-Saharan Africa be also used in middle-income countries like Mexico, or should a new market positioning be defined?

While the answers to these questions are always open to interpretation and speculation, Christensen's Disruptive Theory of Innovation does help in addressing and understanding aspects of them. Once again, it is tempting to enter the CD4 count market in the segment where there is the largest opportunity (i.e. the third segment of need). Nonetheless,

this would mean direct competition against incumbent companies like Becton Dickinson and Beckman Coulter; companies that would very likely win in price battles, distribution capabilities, or even technical and service ability. Successful disruptive models, illustrated by steel mills during the second half of the 20th century and retail medicine clinics in the past decade, have always positioned themselves to address the needs of the otherwise unserved or "overserved" customers.

POC CD4 count device companies, including Daktari, would in principle have significantly higher chances of success if they follow a disruptive-like commercial strategy and market positioning. To this end, the primary target market would be the rather small first segment of need (off-site campaigns). Once a presence is established in this first segment, without yet threatening incumbents, the doors to the other two segments of need will open more easily.

Serving the first segment of need would be of little to no threat to the flow cytometer incumbents. Firstly, the size of the market is presently very small relative to the total number of CD4 count tests in Mexico. Furthermore, flow cytometers simply cannot serve rural, isolated areas (their devices are not portable, and are too expensive to generate any interest among this target market). This first segment, however, can grow significantly from its current size, as recognized and expressed by most interviewees.

Nevertheless, these off-site campaigns are organized and managed by the CAPASITS, which are also the gateways to the other two segments of need, where the larger market opportunity lies. Once physicians, nurses and staff of the CAPASITS become familiarized with the POC CD4 count devices through off-site campaigns, they themselves will become advocates of its implementation in other segments. The opportunity to take CD4 counts at the CAPASITS, and accelerate initiation of ART for patients who urgently need it, will become apparent on its own. Initial experimentation with POC CD4 counts at the CAPASITS will result in obtaining clinical information faster, which will likely result in better patient outcomes and lower patient attrition. This experimentation will become the first stage of an upward migration of POC CD4 count devices towards the second segment of need.

Once a presence is established in the second segment of need (that of CD4 counts at the CAPASITS before ART is initiated), the relative commercial muscle of the disrupting POC

company changes. At this stage, the disruptor is present and established in 30% to 40% of the market for CD4 count tests in Mexico. Suddenly, the notion of replacing those control CD4 counts for patients already in ART (the third segment of need) becomes more plausible, and the possibility of winning a battle against the incumbent flow cytometers is graspable.

By the time the incumbent flow cytometer companies begin to feel threatened, the hold of POC CD4 count diagnostic companies like Daktari is already significant enough to be able to sustain an aggressive head to head competition (if it came to that).

This brief discussion serves to illustrate that the choice of market positioning does make a significant difference in the likely success or failure of POC CD4 count diagnostics. More important, perhaps, is the realization that there must not necessarily be significant changes from the market positioning seen in low-income countries when planning to enter middle-income countries. The same low-end disruption model could apply to either low-income or middle-income countries.

Chapter 6: Conclusions

Concluding Statements

The discussions and evaluations performed throughout this study arrived at several preliminary conclusions worth summarizing and synthesizing. Primary interview sources across the Mexican healthcare spectrum (see **Figure 3-1**) served as the main tools for drawing conclusions and making relevant inferences.

The first primary postulation of this thesis hypothesized a relevant unmet medical need for point-of-care CD4+ T cell count diagnostics in the Mexican HIV/AIDS landscape. After discussing the relevant avenues for identifying and treating HIV/AIDS patients in Mexico, it was determined that the need for POC CD4 count diagnostics does not reside in the Mexican Social Security healthcare system organizations (such as IMSS, ISSSTE, SEDENA, SEMAR or PEMEX). IMSS-Oportunidades, a seemingly ideal organization for implementing POC diagnostics, was also dismissed as a major place for introducing POC CD4 count diagnostics. It was found that the unmet medical need for treating HIV/AIDS patients resided within the state level Secretary of Health infrastructure, through its operating clinics CAPASITS, and the Seguro Popular as the funding mechanism.

Within this CAPASITS network, three major segments of need were identified as the targets for POC CD4 count diagnostics. The first segment of need resides in off-site proactive campaigns where HIV/AIDS patients are diagnosed and treated in rural and isolated regions of Mexico. This segment represents the highest medical need. The second segment on need views the POC CD4 count measurement as a complementary test (in addition to the flow cytometer tests that are ordered at the State Laboratories) for visiting patients at the CAPASITS not yet requiring ART. The use of POC CD4 count diagnostics in this segment improves patient outcome and decreases loss due to attrition. This segment represents a medium level of need. Finally the third segment of need involves substituting flow cytometer CD4 counts for those patients who have already initiated ART. For this segment, the medical need is low, and the value proposition is primarily economic.

For each of these segments, the relevant "quality" versus "convenience" tradeoff that POC diagnostics embody was discussed and evaluated among interviewees. As a general synthesizing statement, it can be said that there is enthusiasm within the Mexican healthcare stakeholders to introduce POC CD4 count diagnostics, and that the medical need is relevant, albeit not urgent.

The second major postulation of this thesis hypothesized a relevant market size for POC CD4 count diagnostics. A market size baseline of ~115 thousand, with an upper bound of ~197 thousand, CD4 count tests per year was estimated. The sensitivity of that baseline to increasing to the estimated upper bound was subject to several factors, including but not limited to the inherent enthusiasm for decentralization of the healthcare system, the expansion of the Seguro Popular, patient adherence to control visits every four months, and competitive resistance from flow cytometer firms. The number of platform devices was also estimated, arriving at a reasonable lower bound of 36 to 68 devices, and an upper bound of 80 to 150 devices.

Furthermore, a review of competitor profiles was brought forward, and a brief discussion of competitive forces and market positioning was conducted. Important competitive factors like pricing, technical specifications, diagnostics accuracy, equipment reliability, and technical support and services, were highlighted as key determinants of success or failure in the POC CD4 count diagnostics market in Mexico. While many variables remain unknown, and many areas are uncertain, the Daktari CD4 device, it was preliminarily concluded, is well positioned to capture a relevant portion of the identified opportunity and market need.

More importantly, the relevance of regulatory and market positioning choices was emphasized. In addition to all of the competitive factors mentioned, the decision to position the regulatory and market entries as low-end disruptors versus head to head competitors may very well determine, it was postulated, the success or failure of the POC CD4 count diagnostic in Mexico.

Limitations

The postulated hypotheses, it must be emphasized, were evaluated and discussed on a preliminary basis. The goal of these evaluations was not was not to reach statistically significant conclusions, but rather to gather sufficient and knowledgeable impressions from stakeholders, to synthesize such impressions, and to extrapolate them into reasonable conclusions regarding the medical unmet need for POC CD4 count diagnostics. Such preliminary evaluations also served as the basis for quantitatively estimating the size of the medical need.

The collection of interviews that served as the hypotheses evaluating tool was not exhaustive. While not resembling the original, ideal list of interviewees, the interview list did however provide a relevant sample of stakeholders in the Mexican healthcare space and in the HIV/AIDS landscape. In addition to the sample not being exhaustive, the process of selecting of interviewees was not randomized, thus representing a possibly relevant source of bias.

I acknowledge that a larger study may be necessary to validate my conclusions, but I believe that the viewpoints obtained in the present study provide a reasonable and plausible perspective, and may serve Mexican and Latin American healthcare stakeholders in shaping their views and policies regarding *Point-of-Care* diagnostics and disruptive innovation models for medical diagnostics and devices.

Future Research

The interviews and discussions conducted with stakeholders across the healthcare and HIV/AIDS landscape in Mexico provided valuable insights and may serve as a roadmap for follow-up studies with greater resources. Nonetheless, this thesis work can be complemented with future research and data.

As a means to further support market size estimations, a robust survey among Mexican healthcare stakeholders would add confidence to the notion of POC CD4 devices capturing the estimated market opportunity. In particular, surveying decision makers at State Laboratories, at CENSIDA, and at key distributors, would provide solid indications of the potential of POC CD4 count diagnostics companies to capture value.

Gathering viewpoints, via more interviews and surveys, of the regulatory body COFEPRIS, and of potential validation study principal investigators, would help clear some of the uncertainties in the regulatory process. In particular, such surveys would help clarify the potential treatment that POC CD4 count diagnostics would be given, in terms of diagnostic accuracy, vis-à-vis flow cytometers.

Detailed understanding of device and per unit test marginal costs, of both flow cytometers and POC CD4 count diagnostics, would also illuminate the discussion around competitive forces and dynamics. Such cost structures would help forecast potential reactions incumbent flow cytometer companies might show, and provide insights into competitive advantages some of the POC CD4 count diagnostic companies might have with respect to one another. In addition, future quantitative follow-up of revenues, margins, market shares, and costs would elucidate whether POC diagnostics actually migrate up market as disruptive innovations to incumbent firms, or whether they simply stay serving a market niche.

On a medium term basis, repeating a similar study and set of discussions 2-3 years from now, for instance, would clarify the hypotheses postulated and conclusions inferred from this study. The cutting-edge technology nature of POC diagnostics makes it an uncertain healthcare space, and a difficult one to predict. Periodic checkpoints over time, revisiting and restating

hypotheses, would yield a better understanding of the impact POC diagnostics might have in Mexico and, more generally, in Latin America.

Furthermore, interviews could be further extended to include many more stakeholders from the HIV/AIDS landscape of Mexico, as well as from healthcare systems of major Latin American markets like Brazil and Colombia, for instance. The idiosyncrasies of each Latin American market and of each healthcare system, make conducting specific country studies ever more relevant and complementary.

Eventually, a comprehensive study would observe and evaluate the evolution of low-end disruption diagnostics and devices, and their impact in low and middle-income countries. The case of one particular type of diagnostic, while insightful, is certainly not representative of the multiple POC diagnostics and devices that could be implemented. POC diagnostics for disease like hepatitis C and dengue fever, and conditions like preeclampsia, could possibly complement and enhance healthcare in Latin America.

In short, several complementary approaches could be undertaken to further understand the impact that POC diagnostics, and low-end disruption models, may have in improving the access and quality of healthcare in patients worldwide.

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Appendix B: Sample CAPASITS and Sample State Laboratory

Sample CAPASITS

Phlebotomy Room

Stock Room (ARTs refrigerated)

Sample State Laboratory

Main hallway

HIV/AIDS dedicated room (Becton Dickinson FACSCalibur flow cytometer visible, left side)