Celebrating 10 Years

Loss to Initiation and Linkage to Care

Bruce Larson, Kate Schnippel, Lawrence Long, Matthew Fox

on behalf of the LTI team

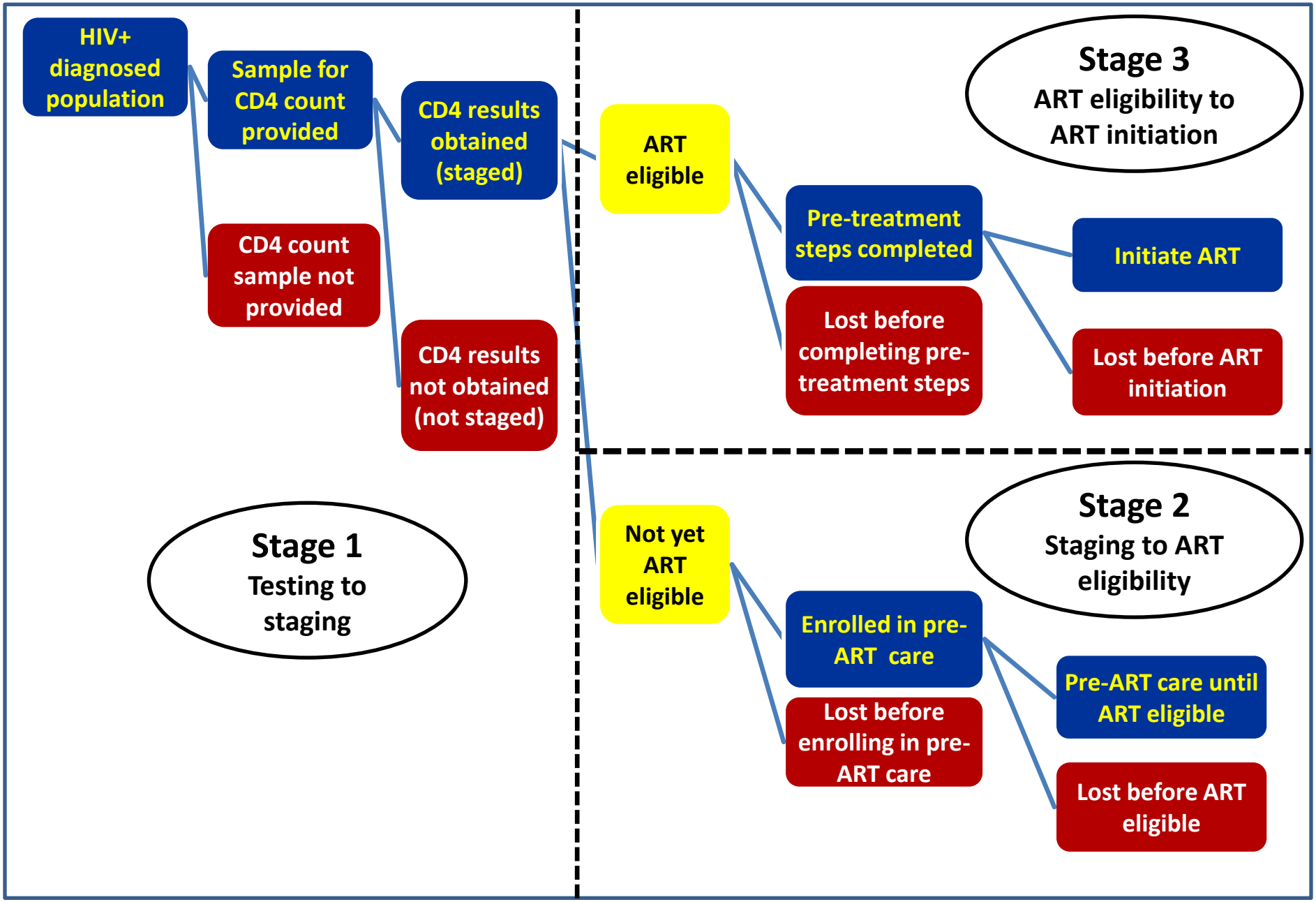
Health Economics and Epidemiology Research Office

Center for Global Health and Development

History

- USAID South Africa was an early mover on the issue of linkage to care
- Substantial published data on post-ART retention in but little published data on pre-ART period
  - May be because emergency response focused on ART (eligibility and treatment guidelines clear)
  - Management guidelines in pre-ART period less developed
  - Also likely because the stages of pre-ART care and measures of pre-ART retention have not been well defined

From Testing to Treatment Initiation



Loss to Initiation

Baseline analyses

Point-of-care CD4 count evaluations

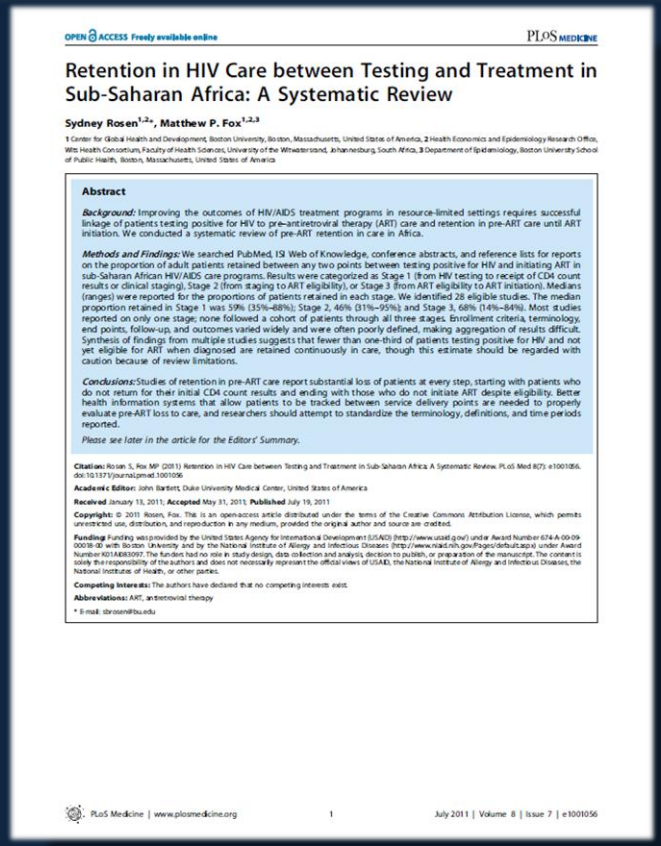
New ideas

Baseline Analyses

Topic	Status	Comments
Systematic review	**Systematic review of pre-ART retention**	**Rosen PLoS Medicine 2011**
Staging to medical visit	Estimate baseline loss between CD4 results and first medical visit at TLC	Larson TMIH 2010
Testing to CD4 staging	**Estimate baseline loss between HIV test and CD4 results at TLC**	**Larson WHO Bull 2010**
Pregnant women	**Pre-ART retention for pregnant women**	**Clouse TMIH 2013**
Definitions	Defining retention in stages of pre-ART care	Fox TMIH 2012
All patients	A complete picture of pre-ART retention	Clouse JAIDS 2013

Review of the Evidence

- Systematic review from March 2011
  - PubMed, ISI Web of Knowledge, conference abstracts
- Included reports of % of adult patients retained between any two points between testing HIV positive and ART initiation
  - Limited to sub-Saharan Africa
- Included 28 studies with quantitative data on at least one pre-ART stage
  - Only 7 countries represented, 1/2 conducted in South Africa



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Retention in HIV Care between Testing and Treatment in Sub-Saharan Africa: A Systematic Review

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Abstract

Background: Improving the outcomes of HIV/AIDS treatment programs in resource-limited settings requires successful linkage of patients testing positive for HIV to pre–antiretroviral therapy (ART) care and retention in pre-ART care until ART initiation. We conducted a systematic review of pre-ART retention in care in Africa.

Methods and Findings: We searched PubMed, ISI Web of Knowledge, conference abstracts, and reference lists for reports on the proportion of adult patients retained between any two points between testing positive for HIV and initiating ART in sub-Saharan African HIV/AIDS care programs. Results were categorized as Stage 1 (from HIV testing to receipt of CD4 count result or clinical staging), Stage 2 (from staging to ART eligibility), or Stage 3 (from ART eligibility to ART initiation). Medians (ranges) were reported for the proportions of patients retained in each stage. We identified 28 eligible studies. The median proportion retained in Stage 1 was 59% (35%–88%); Stage 2, 46% (31%–95%); and Stage 3, 68% (14%–84%). Most studies reported on only one stage; none followed a cohort of patients through all three stages. Enrollment criteria, terminology, end points, follow-up, and outcomes varied widely and were often poorly defined, making aggregation of results difficult. Synthesis of findings from multiple studies suggests that fewer than one-third of patients testing positive for HIV and not yet eligible for ART when diagnosed are retained continuously in care, though this estimate should be regarded with caution because of review limitations.

Conclusions: Studies of retention in pre-ART care report substantial loss of patients at every step, starting with patients who do not return for their initial CD4 count results and ending with those who do not initiate ART despite eligibility. Better health information systems that allow patients to be tracked between service delivery points are needed to properly evaluate pre-ART loss to care, and researchers should attempt to standardize the terminology, definitions, and time periods reported.

Please see later in the article for the Editors' Summary.

Citation: Rosen S, Fox MP (2011) Retention in HIV Care between Testing and Treatment in Sub-Saharan Africa: A Systematic Review. PLoS Med 8(7): e1001056. doi:10.1371/journal.pmed.1001056

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Abbreviations: ART, antiretroviral therapy

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Review of the Evidence

Stage	Outcome	Number of observations	Median [range]
Stage 1—HIV testing to staging	Received CD4 count results		
Stage 2— Staging to ART eligibility	Remained in pre-ART care until repeat CD4 count, ART initiation, or data censoring		
Stage 3—ART eligibility to ART initiation	Initiated ART		

Source: Rosen S, Fox MP (2011) Retention in HIV care between testing and treatment in sub-Saharan Africa: A systematic review. *PLOS Med*; in press.

Retention among Pregnant Women

- Observational cohort study
  - Witkoppen Health and Wellness Center
- Included all pregnant women
  - 18 years
  - Testing HIV+ for the first time at first ANC visit
  - Between January and June 2010
- Total N was 300 pregnant women
- Followed to see outcomes in relation to ART and pregnancy

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Loss to follow-up before and after delivery among women testing HIV positive during pregnancy in Johannesburg, South Africa

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Abstract

OBJECTIVE HIV-positive pregnant women are at heightened risk of becoming lost to follow-up (LTFU) from HIV care. We examined LTFU before and after delivery among pregnant women newly diagnosed with HIV.

METHODS Observational cohort study of all pregnant women ≥18 years ($N = 300$) testing HIV positive for the first time at their first ANC visit between January and June 2010, at a primary healthcare clinic in Johannesburg, South Africa. Women ($n = 27$) whose delivery date could not be determined were excluded.

RESULTS Median (IQR) gestation at HIV testing was 26 weeks (21–30). Ninety-eight per cent received AZT prophylaxis, usually started at the first ANC visit. Of 139 (51.3%) patients who were ART eligible, 66.9% (95% CI 58.8–74.3%) initiated ART prior to delivery; median (IQR) ART duration pre-delivery was 9.5 weeks (5.1–14.2). Among ART-eligible patients, 40.5% (32.3–49.0%) were cumulatively retained through 6 months on ART. Of those ART-ineligible patients at HIV testing, only 22.6% (95% CI 15.9–30.6%) completed CD4 staging and returned for a repeat CD4 test after delivery. LTFU (≥1 month late for last scheduled visit) before delivery was 20.5% (95% CI 16.0–25.6%) and, among those still in care, 47.9% (95% CI 41.2–54.6%) within 6 months after delivery. Overall, 57.5% (95% CI 51.6–63.3%) were lost between HIV testing and 6 months post-delivery.

CONCLUSIONS Our findings highlight the challenge of continuity of care among HIV-positive pregnant women attending antenatal services, particularly those ineligible for ART.

keywords HIV/AIDS, pregnant, antenatal, loss to follow-up, retention, South Africa

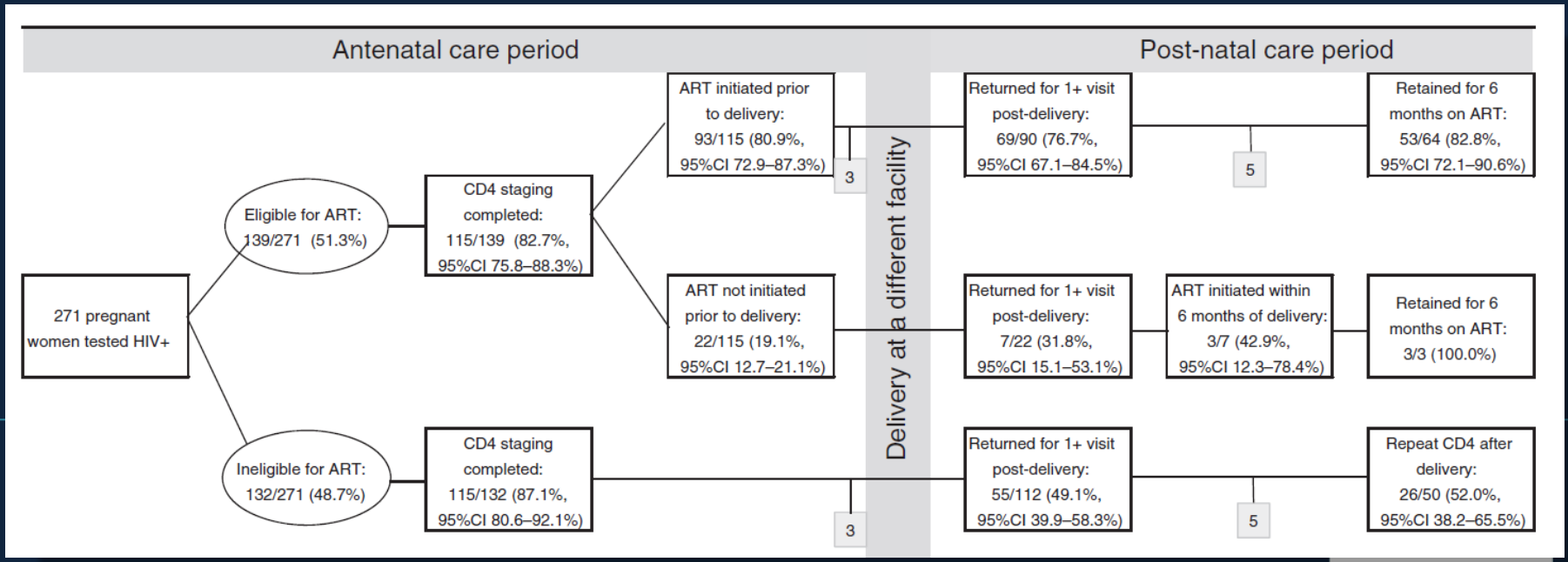
Introduction

South Africa has a national antenatal HIV prevalence of 30.2% (Republic of South Africa Department of Health 2010a) and more people living with HIV than any other country in the world (UNAIDS 2010). In an ongoing effort to improve care for pregnant women with HIV and to prevent mother-to-child transmission (PMTCT), South Africa's 2010 HIV treatment guidelines called for lifelong ART to be initiated for all pregnant women with a CD4 value ≤350 cells/μl (Republic of South Africa Department of Health 2010b) and PMTCT guidelines mandated AZT prophylaxis from 14 weeks of pregnancy (Republic of South Africa Department of Health 2010c). However, implementation of these guidelines remains inadequate, with pregnant women in South Africa commonly presenting for their first ANC visit well into their second trimester or later, delaying HIV diagnosis, AZT prophylaxis and lifelong ART initiation (Black *et al.* 2008; Hoffman *et al.* 2010; Stinson *et al.* 2010).

In addition to late presentation for ANC services, some studies suggest that pregnant women have poorer retention in HIV care than men and non-pregnant women (Kaplan *et al.* 2008; Wang *et al.* 2011). Retention in HIV care is paramount, as HIV-positive patients require routine management and daily adherence to ART once initiated (Republic of South Africa Department of Health 2010d); mortality is high among patients who drop out

Retention among Pregnant Women

- Overall LTFU 57.5% from testing HIV+ at ANC to 6 months postpartum
- LTFU much higher after delivery (47.9%) than prior to delivery (20.5%)
- <70% of ART-eligible women initiated prior to delivery
- Poorest retention among those with CD4 >350 cells/µl



Pre-ART Retention

- Estimated the proportion of walk-in clients at Themba Lethu's VCT program testing HIV+ who returned within 12 weeks for CD4 test results
  - CD4 testing was considered complete once a patient had retrieved the test results
- Retrospective review between January 2008 and February 2009
  - 416 walk-in VCT patients tested positive during study period

Research

Lost opportunities to complete CD4+ lymphocyte testing among patients who tested positive for HIV in South Africa

Bruce A Larson,[a] Alana Brennan,[a] Lynne McNamara,[b] Lawrence Long,[c] Sydney Rosen,[a] Ian Sanne[b] & Matthew P Fox[a]

Objective To estimate rates of completion of CD4+ lymphocyte testing (CD4 testing) within 12 weeks of testing positive for human immunodeficiency virus (HIV) at a large HIV/AIDS clinic in South Africa, and to identify clinical and demographic predictors for completion.
Methods In our study, CD4 testing was considered complete once a patient had retrieved the test results. To determine the rate of CD4 testing completion, we reviewed the records of all clinic patients who tested positive for HIV between January 2008 and February 2009. We identified predictors for completion through multivariate logistic regression.
Findings Of the 416 patients who tested positive for HIV, 84.6% initiated CD4 testing within the study timeframe. Of these patients, 54.3% were immediately eligible for antiretroviral therapy (ART) because of a CD4 cell count ≤ 200/µl, but only 51.3% of the patients in this category completed CD4 testing within 12 weeks of HIV testing. Among those not immediately eligible for ART (CD4 cells > 200/µl), only 14.9% completed CD4 testing within 12 weeks. Overall, of HIV+ patients who initiated CD4 testing, 65% did not complete it within 12 weeks of diagnosis. The higher the baseline CD4 cell count, the lower the odds of completing CD4 testing within 12 weeks.
Conclusion Patient losses between HIV testing, baseline CD4 cell count and the start of care and ART are high. As a result, many patients receive ART too late. Health information systems that link testing programmes with care and treatment programmes are needed.

Une traduction en français de ce résumé figure à la fin de l'article. At the end of the article is a translation in Spanish. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Although access to antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) in South Africa has increased dramatically since 2004, the majority of patients with HIV infection initiate care and treatment with very low CD4+ lymphocyte (CD4 cell) counts, often after they are already symptomatic and long after they are first eligible for ART. During 2009 in South Africa, eligibility for ART was determined by a CD4 cell count ≤ 200 cells/µl or by World Health Organization (WHO) Stage IV condition.[1] A recent analysis in the Free State province showed that more than half of the patients enrolled in the public sector HIV/AIDS treatment programme began ART with a CD4 cell count < 100 cells/µl.[2] Similarly, in an analysis at a large public-sector treatment facility in Johannesburg, 53% of a random sample of patients who started ART in 2005 had a baseline CD4 cell count < 100 cells/µl.[3] More recent data from the same facility showed that the median CD4 cell count was 98 cells/µl for all patients who started therapy during 2007–2008, with 25% having a CD4 cell count < 34 cells/µl (A Brennan, unpublished data, 2009).

Starting care and treatment for HIV infection and AIDS in patients with a low CD4 cell count imposes unnecessary costs on patients and society.[4] Costs to patients include additional morbidity and mortality from HIV- and AIDS-related illnesses and a worse prognosis after initiating ART. Numerous studies have shown that a low CD4 cell count (≤ 100 cells/µl) and WHO Stage IV at the start of treatment are major predictors of mortality.[5–7] Immune system recovery after 3 years on ART is also positively correlated with a patient's CD4 cell count when ART is begun.[8] Access to care and treatment among patients with very low CD4 cell counts is associated with additional health care utilization costs to society through outpatient and inpatient services for opportunistic infections and AIDS-related illnesses. A portion of these costs could be avoided through earlier access to HIV care and treatment, since a substantial share of health care is paid for by the government.

For an HIV+ individual to initiate ART as early as eligibility criteria allow, a specific sequence of events must be completed, starting with HIV testing to diagnose the infection, a baseline CD4 cell count and enrolment in a care programme with regular CD4 cell monitoring, and ending with initiation of ART. In recent years access to HIV testing has increased dramatically, and a recent national survey found that more than half of all South African adults have been tested at least once.[9] This expansion of testing, however, has not translated into earlier treatment initiation.[2,3] One likely reason for this is that people who test positive do not always complete CD4 testing after their HIV test. Because of delays in the completion of CD4 testing, further delays occur in obtaining appropriate care and treatment.

CD4 testing involves two steps. First a blood sample is obtained from the patient at a clinic. In South Africa the blood sample is typically then sent to an external laboratory for analysis, and the results are usually available to the clinic in 1 week. For the purposes of the analysis in this article, CD4 testing was considered complete when a patient actually returned to the clinic and obtained the results. At combined voluntary HIV counselling and testing (VCT) and HIV/AIDS clinics, patients are typically tested for a baseline CD4 cell count on the day they test positive for HIV, although they may return for CD4 testing at a later date. When a stand-alone HIV testing centre does not

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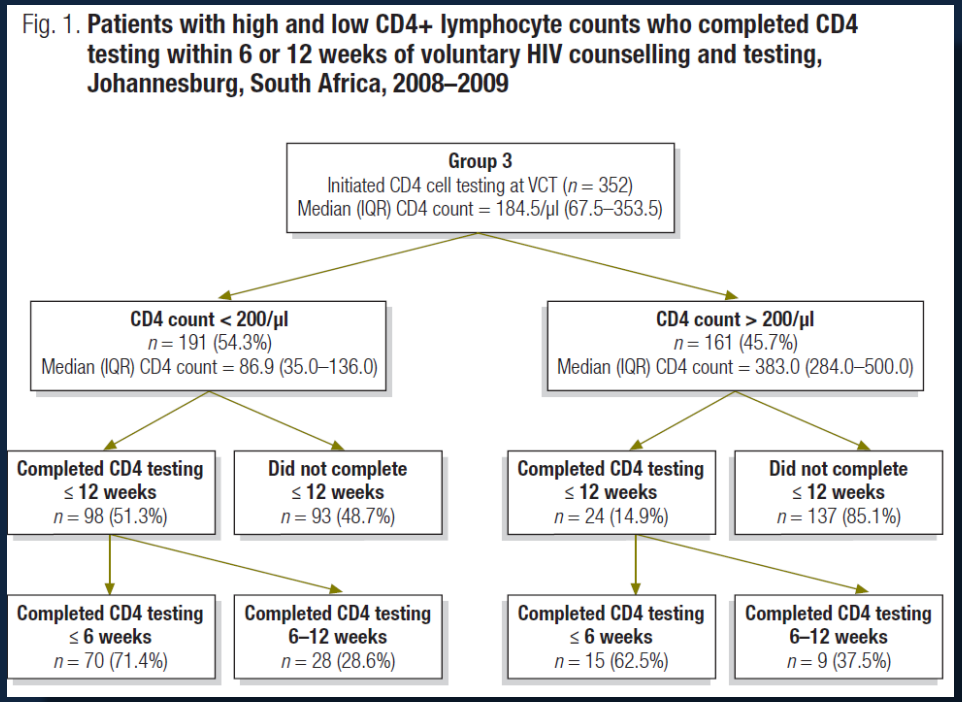
Pre-ART Retention

- Of 416 patients testing +, 84.6% had a CD4 test
- 54.3% were ART eligible (CD4 ≤ 200)
  - 51.3% completed CD4 testing within 12 weeks testing
- Of those not ART eligible
  - 14.9% completed CD4 testing within 12 weeks
- Overall, of those initiating CD4 testing, 65% did not complete within 12 weeks

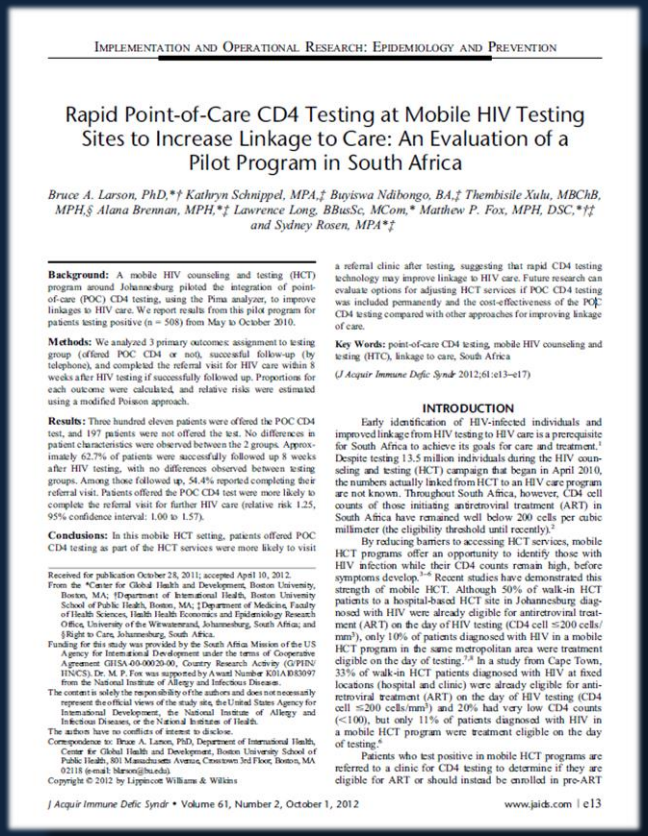


Point-of-Care CD4 Count Evaluations

Project	Project	Status
BD CD4	Evaluation of point-of-care CD4 count technology (BD) at Themba Lethu Clinic	Larson AIDS Res and Treat 2013
PIMA	Evaluation of point-of-care CD4 count technology (Pima) at RTC mobile HIV testing sites	Larson JAIDS 2012
Multiple POC technologies	Rapid treatment initiation to improve HIV treatment outcomes	Ongoing

PIMA Testing to Reduce LTI

- Objective
  - Evaluate if addition of POC PIMA CD4 testing at HCT improved post-HCT linkage to care and treatment
- Quasi-experimental design
  - Used a pre-post analysis
- Primary outcome:
  - Completed referral visit within 8 weeks after testing



IMPLEMENTATION AND OPERATIONAL RESEARCH: EPIDEMIOLOGY AND PREVENTION

Rapid Point-of-Care CD4 Testing at Mobile HIV Testing Sites to Increase Linkage to Care: An Evaluation of a Pilot Program in South Africa

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Background: A mobile HIV counseling and testing (HCT) program around Johannesburg piloted the integration of point-of-care (POC) CD4 testing, using the Pima analyzer, to improve linkages to HIV care. We report results from this pilot program for patients testing positive (n = 508) from May to October 2010.

Methods: We analyzed 3 primary outcomes: assignment to testing group (offered POC CD4 or not), successful follow-up (by telephone), and completed the referral visit for HIV care within 8 weeks after HIV testing if successfully followed up. Proportions for each outcome were calculated, and relative risks were estimated using a modified Poisson approach.

Results: Three hundred eleven patients were offered the POC CD4 test, and 197 patients were not offered the test. No differences in patient characteristics were observed between the 2 groups. Approximately 62.7% of patients were successfully followed up 8 weeks after HIV testing, with no differences observed between testing groups. Among those followed up, 54.4% reported completing their referral visit. Patients offered the POC CD4 test were more likely to complete the referral visit for further HIV care (relative risk 1.25, 95% confidence interval: 1.00 to 1.57).

Conclusions: In this mobile HCT setting, patients offered POC CD4 testing as part of the HCT services were more likely to visit a referral clinic after testing, suggesting that rapid CD4 testing technology may improve linkage to HIV care. Future research can evaluate options for adjusting HCT services if POC CD4 testing was included permanently and the cost-effectiveness of the POC CD4 testing compared with other approaches for improving linkage of care.

Key Words: point-of-care CD4 testing, mobile HIV counseling and testing (HTC), linkage to care, South Africa

(*J Acquir Immune Defic Syndr* 2012;61:e13–e17)

INTRODUCTION

Early identification of HIV-infected individuals and improved linkage from HIV testing to HIV care is a prerequisite for South Africa to achieve its goals for care and treatment.[1] Despite testing 13.5 million individuals during the HIV counseling and testing (HCT) campaign that began in April 2010, the numbers actually linked from HCT to an HIV care program are not known. Throughout South Africa, however, CD4 cell counts of those initiating antiretroviral treatment (ART) in South Africa have remained well below 200 cells per cubic millimeter (the eligibility threshold until recently).[2]

By reducing barriers to accessing HCT services, mobile HCT programs offer an opportunity to identify those with HIV infection while their CD4 counts remain high, before symptoms develop.[3–6] Recent studies have demonstrated this strength of mobile HCT. Although 50% of walk-in HCT patients to a hospital-based HCT site in Johannesburg diagnosed with HIV were already eligible for antiretroviral treatment (ART) on the day of HIV testing (CD4 cell ≤200 cells/mm³), only 10% of patients diagnosed with HIV in a mobile HCT program in the same metropolitan area were treatment eligible on the day of testing.[7,8] In a study from Cape Town, 33% of walk-in HCT patients diagnosed with HIV at fixed locations (hospital and clinic) were already eligible for antiretroviral treatment (ART) on the day of HIV testing (CD4 cell ≤200 cells/mm³) and 20% had very low CD4 counts (<100), but only 11% of patients diagnosed with HIV in a mobile HCT program were treatment eligible on the day of testing.[6]

Patients who test positive in mobile HCT programs are referred to a clinic for CD4 testing to determine if they are eligible for ART or should instead be enrolled in pre-ART

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The authors have no conflicts of interest to disclose.
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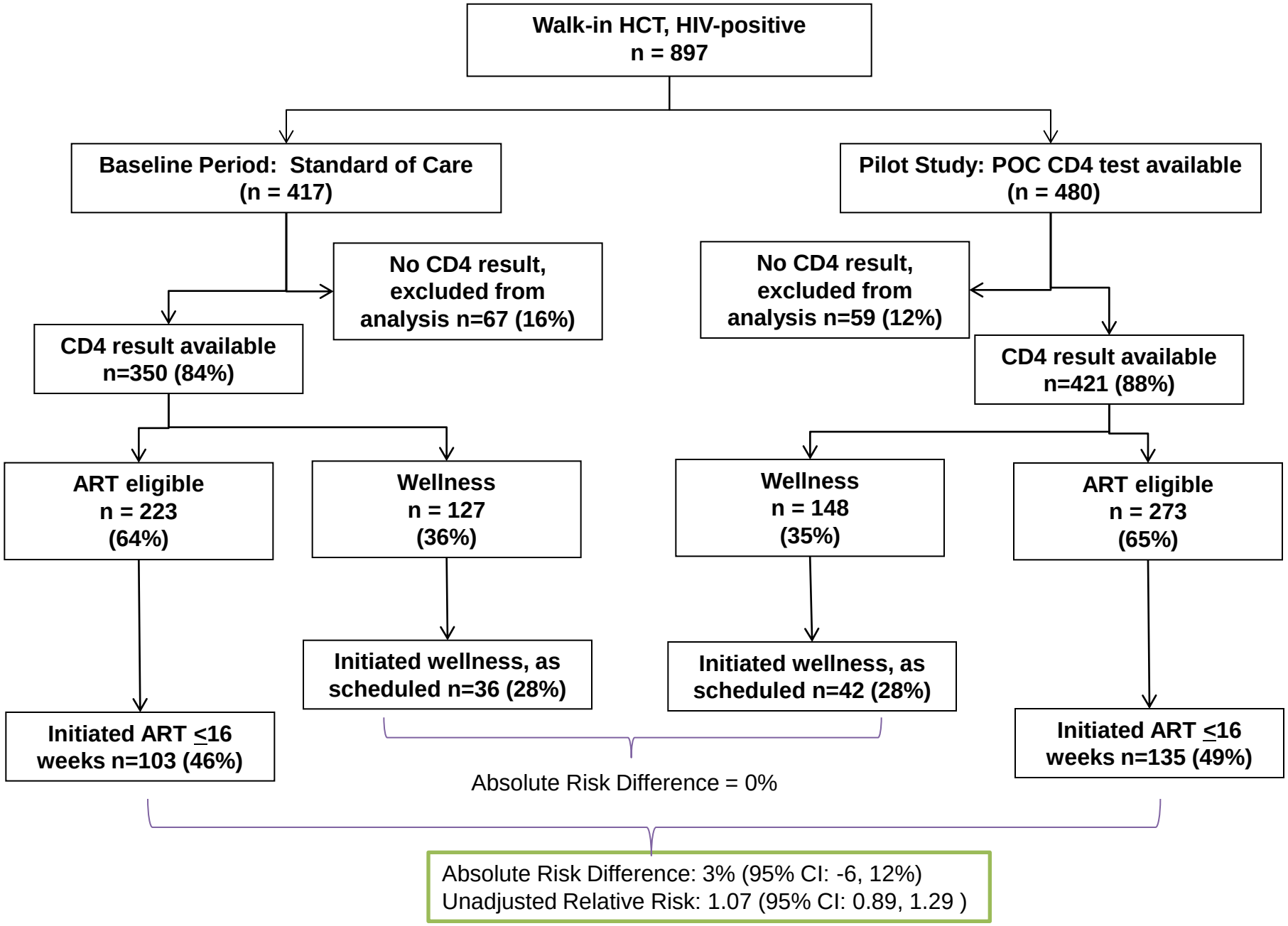
Walk-in HCT, HIV-positive
n = 897
Baseline Period: Standard of Care
(n = 417)
Pilot Study: POC CD4 test available
(n = 480)
No CD4 result, excluded from analysis n=67 (16%)
No CD4 result, excluded from analysis n=59 (12%)
CD4 result available
n=350 (84%)
CD4 result available
n=421 (88%)
ART eligible
n = 223
(64%)
Wellness
n = 127
(36%)
Wellness
n = 148
(35%)
ART eligible
n = 273
(65%)
Initiated wellness, as scheduled n=36 (28%)
Initiated wellness, as scheduled n=42 (28%)
Initiated ART ≤16 weeks n=103 (46%)
Initiated ART ≤16 weeks n=135 (49%)
Absolute Risk Difference = 0%
Absolute Risk Difference: 3% (95% CI: -6, 12%)
Unadjusted Relative Risk: 1.07 (95% CI: 0.89, 1.29)

Lessons Learned

- This is an extremely important issue and failure to pay attention to pre-ART retention means wasted resources and lost opportunities to improve treatment outcomes
  - If post ART retention is hard to measure, this is extremely hard
  - Should have pushed earlier for better ability to track pre-ART retention
- It will be important to follow changes in pre-ART retention in the era of increasing treatment thresholds
  - Could lead to better retention as it eliminates pre-ART care for many patients
- Different interventions may need to be targeted to each time period as reasons for loss at each stage may differ