Electronic medical records and clinical Decision Support Systems in HIV care in resource-limited settings

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This thesis focuses on the use of electronic medical record (EMR) and clinical decision support systems (CDSS) to improve quality of care for HIV/AIDS patients through better adherence to WHO and national clinical guidelines. HIV/AIDS is a major public health problem; in 2013 nearly 35 million people were infected globally, with 71% living in sub-Saharan Africa (SSA). Approximately 1.5 million people died of AIDS-related illnesses in 2013. Kenya is ranked fourth globally in HIV/AIDS burden. We start by describing the biological and socio-behavioral factors associated with HIV infection among adults aged 15-49 years in Kenya. The main studies included in this thesis, based on rigorous scientific design and conducted in Kenya, provide strong evidence that EMR-based CDSS can improve adherence to HIV/AIDS treatment guidelines in resource-limited countries in SSA, and hence quality of care. We show that EMRs and CDSS can significantly improve timely initiation of life-saving antiretroviral therapy and early detection and action on treatment failure among HIV patients. We also describe the process of standardizing the recording of AIDS-Defining Illnesses (ADIs) and derivation of a reference set for ADIs based on an international terminology system (SNOMED CT). The reference set was implemented as an interface terminology of an EMR at a busy teaching and referral hospital in western Kenya.

Overall, the thesis provides compelling evidence that EMR-based CDSS improve quality of HIV care in resource-limited settings.
Electronic Medical Records and Clinical Decision Support Systems in HIV Care in Resource-Limited Settings

Tom Onyango Oluoch
Electronic Medical Records and Clinical Decision Support Systems in HIV Care in Resource-Limited Settings
PhD thesis, University of Amsterdam, Amsterdam, The Netherlands

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Chapter 1

General Introduction
1.1 HIV Epidemic in Kenya

The World Health Organization (WHO) describes the Human Immunodeficiency Virus (HIV) as a retrovirus that infects cells of the host’s immune system and destroys or impairs their function. Acquired Immune Deficiency Syndrome (AIDS) is the disease caused by infection with the HIV. AIDS results in severe damage of the body’s immune system causing vulnerability to life-threatening infections and tumors (1). Heterosexual sex between an HIV infected person and uninfected partner is the main mode of HIV transmission in many sub-Saharan African (SSA) countries (2;3). The WHO and The Joint United Nations Programme on HIV/AIDS (UNAIDS) joint report on global HIV epidemic showed that nearly two-thirds of the 34 million people infected with the virus resided in SSA in 2010 (4). Kenya is among the countries with high HIV prevalence in SSA. The Kenya AIDS Indicator Survey (KAIS) conducted in 2007 showed that HIV prevalence among adults aged 15-64 years was 7.1% (5). A similar population-based survey conducted five years later showed a decline in HIV prevalence to 5.6% (6). The two surveys showed that Nyanza province in western Kenya had the highest HIV prevalence in Kenya with 14.9% and 15.2% of adults aged 15-64 years having HIV-infection in 2007 and 2012, respectively (5;6).

In order to plan for effective interventions to respond to the HIV epidemic, it is necessary to understand the socio-demographic, behavioral and biological factors associated with the disease. Various sources of data including routine statistical summaries, surveys, surveillance, operational research and mathematical modeling are used to monitor the distribution and trends in the epidemic in response to prevention and treatment programs. UNAIDS and WHO have developed guidelines for measuring HIV prevalence in population-based surveys (7). The KAIS protocols were developed based on the UNAIDS/WHO guidelines to provide HIV prevalence data as well as factors associated with HIV infection in Kenya (5;6).

KAIS is a household survey that entails interviewing eligible and consenting respondents from sampled clusters of households. Blood samples are collected from consenting participants for central testing in the laboratory to determine HIV prevalence. Individual participants who wish to know their HIV status can collect their results at the nearest clinic six weeks after blood sample collection, or participate in a voluntary home-based HIV counseling and testing. Those confirmed to be HIV-infected are referred for HIV care and treatment services. KAIS also provides critical data on access to HIV prevention, care and treatment services, respondents’ perception of risk for HIV infection, risk factors for HIV infection and co-morbidities – including sexually transmitted infections.

1.2 HIV Care and Treatment Guidelines

As of December 2011, and to improve quality of lives of those infected with the virus and to prevent further transmission of the virus, approximately 7.9 million patients were receiving Antiretroviral Therapy (ART) globally with 75% (n=6 million) living in SSA (8). As with other diseases that affect global populations, WHO has developed guidelines for care and treatment of persons infected with HIV. Many countries, including Kenya, have adopted these guidelines and customized them to be most appropriate in addressing the local epidemic. In June 2013, WHO launched The Consolidated Guidelines on the Use of
Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach (9). Among other things, the consolidated guidelines address HIV diagnosis and antiretroviral drugs for HIV prevention; linking people diagnosed with HIV to clinical care and treatment; indicating when to start ART, and what ART regimen to start treatment-naïve patients on (first-line ART), monitoring the response to ART and diagnosis of treatment failure; and managing common infections and co-morbidities (including opportunistic infections, which are referred to in this thesis as AIDS Defining Illnesses).

Guidelines released by WHO in 2010 recommended the use of CD4+ T-cell count to assess eligibility for ART and to monitor the immune system’s response to ART (10). CD4+ T-cells are white cells that are an essential part of the body’s immune system. Various studies have shown that CD4+ T-cell count and viral load are the key prognostic factors for HIV disease progression to AIDS and death (11;12). Early mortality is higher among patients enrolling on HIV care with low baseline CD4+ T-cell count (13). The WHO guidelines recommend a baseline measurement of CD4+ T-cells immediately after the HIV patients have a confirmed HIV-positive result, and follow-up measurements every six months (10). The latest guidelines recommend initiating ART when a patient’s CD4+ T-cell count drops to 500 cells/µl (9). Previous revisions of the WHO guidelines recommended initiating ART at CD+4 T-cell counts of 250 cells/µl (10) and 350 cells/µl (14).

The 2006 revision of the WHO guidelines recommended the use of clinical presentation of patients to classify the progression of HIV infection. These guidelines classify common co-morbidities known to be associated with HIV into four clinical stages based on the severity and prognosis that reflect HIV disease progression from asymptomatic to conditions where presumptive diagnoses can be made on the basis of clinical presentation or simple investigations (10). The documentation of these stages helps clinicians in resource-limited settings (mainly in Africa and Asia) with no immediate access to CD4+ T-cell count testing to make decisions on ART eligibility (10).

Immunological treatment failure occurs when there is sub-optimal response by the immune system to ART. One of the main causes of HIV treatment failure is non-adherence by patients to the prescribed drug dosages leading to sub-therapeutic concentration of ART in plasma (15). Treatment failure should be detected at the earliest opportunity and appropriate action such as adherence counseling, viral load test or repeat CD4 test taken.

1.3 Treatment of HIV

Standard ART is a combination of at least three drugs that are taken to suppress the HIV and progression of HIV disease (14). Before a patient becomes eligible for ART, they receive pre-ART care which includes medications to prevent opportunistic infections, multi-vitamins and education on how to stay healthy and avoid infecting others (4). Newly diagnosed HIV patients or those newly enrolled on ART should visit the clinic monthly, while stable patients are expected to attend the clinic every three months for review and medication refills. AIDS, like other chronic diseases, requires lifelong treatment and ongoing collection of longitudinal data to monitor the response to treatment at individual patient level and for
routine statistical reporting. The rapidly increasing number of patients enrolling on HIV treatment in SSA annually, coupled with a limited number of health workers, can potentially compromise the recording of patient data (16) and thereby their care. In order to address this, there is urgent need for innovative solutions such as Electronic Medical Records (EMRs) for the management of the large amounts of longitudinal data, and Clinical Decision Support Systems (CDSS) for providing feedback to health care workers to improve guideline adherence. In particular, studies in developed countries have shown that EMRs and CDSSs are associated with better diagnosis, reduced medication errors, improved data quality and better practitioner performance (17-19).

1.4 Electronic Medical Records

SSA has lagged behind in adopting EMRs and the majority of health facilities still use paper forms to manage patient records. Health facilities in SSA face unique challenges including infrastructural and human capacity limitations. Infrastructural challenges include unreliable or unavailable electric power, inadequate computers and poor or no access to the Internet. Health workers often have limited computer skills. This, coupled with inadequate technical skills to install and maintain computer systems, especially in rural areas where the majority of the patients seek treatment, reduces the ability to utilize information technology (IT) interventions in health care to improve its delivery (20).

Various countries in SSA have benefitted from the support from multilateral (e.g. WHO and UNICEF) and bilateral partners (e.g. The US Government through the President’s Emergency Plan for AIDS Relief - PEPFAR) to access resources for strengthening health systems, including EMRs (21). Since 2010, PEPFAR has funded the implementation of EMRs at approximately 600 health facilities in Kenya, of which a majority is owned by the Kenyan Ministry of Health (MOH).

1.5 Clinical Decision Support Systems (CDSS)

A CDSS is a computer program that applies sets of rules to data, often stored in EMRs, in order to offer patient-specific and actionable recommendations to improve clinical decisions (22). Recommendations of a CDSS are communicated to the EMR user as alerts or reminders. The set of rules implemented in a CDSS often represents guidelines. CDSSs have been shown to have the ability to improve quality of care though better adherence to clinical guidelines, improved patient safety, more efficient clinical processes, and better patient outcomes in developed countries (23;24).

1.6 Quality of Care and of Data

Quality of medical care is difficult to define and measure as it is determined by conceptual and operationalized characteristics of what quality is (25). Process and outcome indicators are often used to measure quality of health care (25;26) and various methods have been adopted to improve the quality of health care through better compliance with clinical guidelines. In HIV care, for example, timely initiation of ART, timely performance of appropriate treatment monitoring measurements using laboratory tests such as CD4+ T-cell counts and viral load are factors that enhance quality of care.
Unstructured collection and recording of free-text key data elements such as diagnoses limits data quality and data re-usability for decision support or statistical analysis as the diagnoses are not uniquely defined and identified with a code (27). A terminology system such as SNOMED CT can contribute to data accuracy and re-use through concept-based definition of diagnoses and coded storage of data (28) hence improved quality of care.

1.7 Problem Statement

The majority of published studies so far that have used rigorous scientific methods to evaluate associations between health IT interventions, such as EMRs and CDSSs, and selected quality of care outcomes were conducted in developed countries. Countries in SSA, which bear the greatest burden of HIV, also have the weakest health systems making it difficult to provide care of high quality. With the increasing investment in health systems including EMRs and other systems in SSA, there is a critical need to evaluate the effect of such systems on quality of care. These evaluations would inform appropriate investments in solutions that address context-specific problems while taking into account unique challenges of implementing health IT interventions in resource-limited settings.

The research work published in this thesis describes HIV epidemiology in Kenya, a systematic review on EMR-based CDSS in resource-limited settings and associations and effects between EMR/CDSS and quality of care in Kenya.

1.8 Research Questions

This thesis addresses the following research questions:

(i) What are the socio-demographic, behavioral and biological risk factors associated with HIV infection among sexually active adults in Kenya?
(ii) Are EMRs associated with enhanced quality of HIV care and treatment in resource-limited settings?
(iii) What is the effect of CDSS on quality of HIV care and treatment in resource-limited settings?
(iv) Does SNOMED CT cover AIDS defining illnesses and can it be used to develop and implement an interface terminology in an EMR in a busy HIV clinic in sub-Saharan Africa in order to automatically derive WHO clinical staging of HIV?
1.9 Thesis Outline:

The research questions listed above were addressed through several studies that were conducted in the Nyanza region in western Kenya. Additionally, a national population-based survey provided epidemiologic data. The findings from these studies are presented in the chapters described below.

In chapter 2, we describe an epidemiologic study that was designed to address question (i). It provides a broad overview of the distribution of the HIV epidemic and factors for HIV infection among sexually active adults in Kenya.

Research question (ii) is addressed through two chapters. Chapter 3 describes the findings of a study on adherence to pre-ART guidelines following the introduction of an EMR in 17 clinics in western Kenya. In chapter 4, we present the results of a multi-center study evaluating the association between EMR and appropriate placement/initiation of HIV-infected patients on ART. The study was conducted in the same 17 health facilities described in the previous chapter. Research question (iii) is addressed through chapters 5 and 6. In chapter 5 we describe the results of a systematic review of published papers on the effects of EMR-based CDSS on quality of HIV care in resource-constrained settings. Chapter 6 describes the findings of a multi-center cluster randomized controlled trial to assess the effect of EMR-based CDSS on early detection of immunological treatment failure among HIV-infected patients at 13 clinics in western Kenya. The study presents the implementation of a CDSS to detect immunological treatment failure in compliance with the treatment guidelines and recommending appropriate clinical action.

To address research question (iv), chapter 7 describes the development of a SNOMED CT-based reference set for AIDS-Defining Illnesses (ADI) and its implementation as an interface terminology for OpenMRS EMR at a Kenyan teaching and referral hospital.

Finally, the overall synthesis of the key findings from the studies presented in this thesis and recommendations for further research are presented in a summary discussion in chapter 8. Figure 1.1 shows the stages at which the studies in this thesis support patient care.

Figure 1.1: The flow of patients from HIV infection to monitoring treatment and the stages at which various studies in this thesis were conducted.
Reference List

(10) World Health Organization. WHO Case Definitions of HIV For Surveillance and Revised Clinical Staging and Immunological Classification of HIV-related Disease in Adults and Children. 2006.


Chapter 2

Correlates of HIV infection among sexually active adults in Kenya: a national population-based survey

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Abstract

Objective
To identify factors associated with prevalent HIV in a national HIV survey in Kenya.

Methods
The Kenya AIDS Indicator Survey (KAIS) was a nationally representative population-based sero-survey that examined demographic and behavioral factors and serologic testing for HIV, HSV-2, syphilis, and CD4 cell counts in consenting adults aged 15-64 years. We analyzed questionnaire and blood testing data to identify significant correlates of HIV infection among sexually active adults.

Results
Of 10,957 eligible women and 8,883 men, we interviewed 10,239 (93%) women and 7,731 (87%) men. We collected blood specimens from 9,049 women and 6,804 men of which 6,447 women and 5,112 men were sexually active during the 12 months prior to the survey. HIV prevalence among sexually active adults was 7.4%. Factors independently associated with HIV among women were region (Nyanza vs Nairobi: adjusted OR [AOR] 1.6, 95% CI 1.1-2.3), number of lifetime sex partners (4-5 vs 0-1: AOR 2.3, 95% CI 1.6-3.5), HSV-2 (AOR 6.5, 95% CI 4.9-8.8), marital status (separated/divorced vs. never married: AOR 2.2, 95% CI 1.2-3.9) and consistent condom use with the last sex partner (AOR 2.3, 95% CI 1.6-3.4).

Among men, correlates of HIV infection were 30-to-39-year-old age group (AOR 5.2, 95% CI 2.6-10.5), number of lifetime sex partners (10+ vs 0-1 partners, AOR 3.5, 95% CI 1.4-9.0), HSV-2 (AOR 4.7, 95% CI 3.2-6.8), syphilis (AOR 2.4, 95% CI 1.4-4.0), consistent condom use with the last sex partner (AOR 2.1, 95% CI 1.5-3.1) and lack of circumcision (AOR 4.0, 95% CI 2.8 - 5.5).

Conclusion
Kenya’s heterogeneous epidemic will require regional and gender-specific prevention approaches.
2.1 Introduction

Lack of a comprehensive understanding of national HIV epidemics remains a major challenge for targeting effective HIV programs. Antenatal clinic (ANC) sentinel surveillance has been useful to document trends of generalized epidemics but lacks adequate sexual-behavioral and other associated risk factors for HIV infection, and is not generalizable to men and non-pregnant women (1). Studies conducted in a number of sub-Saharan African countries showed that ANC data over-estimated prevalence in 15-19 year olds and under-estimated prevalence in older ANC clinic attendees (2;3). Hospital-based studies have also been conducted in low prevalence areas to understand risk factors (4), but the findings are not easily generalizable to populations living in countries with high HIV prevalence.

Concerns about the representativeness and accuracy of national HIV estimates derived from ANC surveillance have led to an increased demand for surveys and more data on the prevalence and distribution of HIV in the whole population (5). In sub-Saharan Africa, more than 38 countries have conducted national population-based HIV surveys (6). These surveys most often were restricted to reproductive ages, collected dried blood spots for biological tests (7), and avoided questions about sexual behavior and HIV status which are considered sensitive. Thus, laboratory and risk factor analyses have been limited. Programmatic data from voluntary counseling and testing (VCT) centers as well as HIV test results from prevention of mother-to-child transmission (PMTCT) programs have been used in some cases to estimate HIV prevalence and investigate associations with demographic, behavioral, and biological factors (8-10). However, these are limited due to their lack of representativeness of the populations that seek VCT and PMTCT services (11). For example, PMTCT services are only offered to pregnant women. Additionally, risk behavior, perception of risk behavior, or attitudes towards HIV/AIDS have been shown to influence uptake of VCT services (12).

Sexual transmission is the major route for HIV infection in sub-Saharan Africa (13;14). In Kenya, sexual transmission contributes over 90% of all HIV infections (13). The World Health Organization (WHO) categorizes Kenya as having a generalized HIV epidemic, defined as having an HIV prevalence of more than 1% in the adult general population and more than 5% in vulnerable adults such as sexually transmitted infection (STI) clinic patients. Kenya has wide variability in the distribution of HIV infection by geographic, demographic, sexual-behavioral, and biological factors. The Kenya Demographic and Health Survey (KDHS) conducted in 2003 included HIV serology but was limited in the scope and depth of sexual-behavioral and biological indicators collected, and included consenting adults aged 15-49 years (15). In this era of expansion of prevention, care and treatment programs for HIV, additional variables of interest are needed to facilitate accurate interpretation of HIV prevalence data and associated risk factors (16).

We conducted the Kenya AIDS Indicator Survey (KAIS) in 2007 to provide nationally-representative and comprehensive data on demographic, behavioral, and biologic indicators of HIV/AIDS, beyond that of previous national HIV surveys in Kenya. In addition to providing national prevalence estimates for HIV and sexually transmitted infections, these data provided the opportunity to link HIV status with key demographic, behavioral, and biologic information to identify significant correlates associated with HIV infection in Kenya. We examined factors independently associated with the risk of HIV infection among individuals who were sexually active during the 12 months prior to the survey.
2.2 Methods

2.2.1 Ethics Statement

Ethical approval was obtained from the Ethical Review Committee at the Kenya Medical Research Institute (KEMRI) and the Institutional Review Board at the Centers for Disease Control and Prevention (CDC). Respondents provided consent separately for the interviews and blood draws.

2.2.2 Study setting

KAIS was conducted among a nationally representative sample of households selected from all the eight provinces in Kenya, covering both rural and urban areas. Various studies show that Nyanza province continues to have the highest HIV prevalence in Kenya (15;17;18). Nairobi province is the capital city and has a cosmopolitan population with diverse ethnic groups and cultures. Nyanza on the other hand is predominantly inhabited by the Luo ethnic group.

2.2.3 Survey Design, Sampling and Participation

Briefly, we conducted a cross-sectional, stratified two-stage cluster survey designed to achieve a nationally representative sample and sufficient statistical power to provide prevalence estimates for each of the 8 provinces. The first stage involved selecting 415 clusters out of 1,800 in the national sampling frame and the second stage involved the selection of households per cluster with equal probability of selection in the rural-urban strata. In order to reflect the population distribution, we sampled 294 and 121 clusters in rural and urban areas respectively. We collected data between August and December, 2007. Eligible participants were individuals aged 15-64 who were residents or household visitors the night prior to the survey team’s visit. We administered household and individual questionnaires and collected venous blood from respondents. Key questions included respondent’s HIV status, testing history, age at sexual debut, condom use, number of lifetime sex partners, alcohol use during last sexual intercourse, male circumcision status and mobility (which was defined as the number of separate occasions when the respondent traveled away from home/community and slept away in the previous 12 months) and access to cotrimoxazole and antiretroviral therapy (ART) for those with HIV infection. Partner-specific information on HIV status, testing history, disclosure, condom use and family planning preference were collected for up to four sex partners in the last year. With exception of condom use and family planning preferences, many of the indicators were unique to KAIS and were not asked in the KDHS. For population size estimates, we used census data from the Kenya National Bureau of Statistics, using the 2006 sampling frame based on the 1999 census. We calculated the corresponding 95% confidence intervals taking into account the sampling weights and study design. Full details of methods used in KAIS have been published elsewhere (18).

2.2.4 Laboratory testing

Blood specimens were transported to Kenya’s National Public Health Laboratory in Nairobi and tested for HIV, syphilis and HSV-2. CD4 cell count enumeration was conducted for HIV-infected participants. HIV testing was performed according to the national guidelines for HIV testing using a validated HIV testing algorithm for the country: the Vironostika HIV Uni-Form II antigen/antibody (BioMérieux Bv, Boeind, Netherlands) for screening and the Murex HIV antigen/antibody combination (Abbott/Murex-Biotech Ltd, Kent, UK) for confirmation in a serial testing algorithm. Specimens with discordant results were re-tested with the two assays. Polymerase Chain Reaction (PCR) testing was conducted on
specimens that still had two discordant results after re-testing. For HSV-2 testing, the Kalon HSV Type 2-specific IgG EIA (Kalon Biologicals, Guildford, UK) was used; this was a recombinant type 2 antigen (gG2) modified to eliminate reactivity arising from HSV type 1 infection, at the same time retaining the natural antigenic characteristics of HSV-2. For syphilis infection, serum specimens were first screened using a *Treponema pallidum* particle agglutination assay (TPPA) (Serodia-TPPA, Fujirebio Diagnostics Inc, Tokyo, Japan) to detect previous exposure to syphilis antigens. All TPPA-positive specimens were then tested using a rapid plasma reagin (RPR) (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) test on undiluted (i.e. neat) serum specimen to test for reaginic antigens. Specimens with positive TPPA and RPR serologies were defined an active syphilis infection. For quality control of each test, all positive specimens and 5% of negative specimens were retested in a different laboratory using the same testing algorithms.

### 2.2.5 Data analysis

Data from questionnaires were entered into a CSPro database (version 3.3, US Census Bureau, Washington DC, USA) by two different data clerks. All discrepancies between the two entries were resolved by a data manager during the data cleaning stage. To obtain nationally representative estimates, we calculated sampling weights for each individual and household based on selection probability and taking into account cluster-level non-participation. In addition, special weights were calculated for those who participated in the blood draw to take into account cluster-level non-participation.

For the purposes of this paper, we restricted this analysis to a sub-set of questions from the individual questionnaire among participants who were sexually active in the last year before the survey. Sexually active individuals were those who self-reported having had sexual intercourse. Additionally, we conducted a sub-analysis to further investigate correlates of HIV infection that were specific to Nyanza province, the province with the highest HIV prevalence rate for men and women compared to all other provinces. We used the Rao-Scott chi-square test which allowed adjusting for the cluster survey design when testing for associations between categorical variables and HIV infection. Bivariate analysis was used to quantify the association between the demographic, behavioral and biological variables and HIV infection. We conducted multivariate logistic regression by constructing separate models for males and females to assess factors independently and significantly associated with HIV infection among sexually active persons. All variables were first included in the models and model selection was carried out using a backward elimination procedure. All variables that had a p-value of greater than 0.5 were removed from the models in the first step unless they were suspected to be confounders. Variables were then removed sequentially from the models starting with the one with the highest p-value until all variables had a p-value of less than 0.05. All confounders were retained in the model irrespective of the p-value. Odds ratios, adjusted odds ratios (AOR), and associated 95% confidence intervals were calculated based on pre-specified reference groups.

### 2.3 Results

We collected information from 9,691 households. A total of 19,840 individuals were eligible, of which 17,970 (90%) consented to be interviewed, including 10,239 women (93%) and 7,731 men (87%) (Figure 2.1). Among the eligible respondents, 9,049 (83%) women and 6,804 (77%) men consented for and provided a blood sample for HIV, HSV-2, and syphilis testing, a response rate of 88% of those interviewed, with similar uptake rates among men and women. Among those consenting to blood draw 6,447 women (71%) and 5,112 men (75%) were sexually active in the last year. Overall, 57% of KAIS
Figure 2.1: Study Profile

402 Enumeration areas randomly selected from 2003 KDHS
285 Rural clusters

10,050 households contacted

359 households refused participation or members were repeatedly absent

9,691 households participated

19,840 Eligible adults (15-64 years)
10,957 Women

1,870 Refused or absent

17,970 Interviewed
10,239 Women

2,117 Refused or absent for HIV testing

15,853 Tested
9,049 Women

11,559 sexually active at least 12 months prior to the survey
6,447 Women
participants were female, the median age was 30 years, 74% resided in rural areas, 70% were currently employed, 61% were married, and <1% of women and 6.6% of men drank alcohol before their last sexual encounter (Table 2.1). Among the laboratory-confirmed HIV positive respondents, 56% had never tested for HIV infection, 28% self-reported HIV negative and 16% self-reported HIV positive status. We found ethnicity to be co-linear with province and circumcision and choose to present differential risks with a focus on circumcision status and province rather than with a focus on ethnicity.

2.3.1 HIV prevalence

Overall, HIV prevalence among all adults aged 15-64 years was 7.1% (95% CI, 6.5-7.7), representing an estimated 1.4 million people nationwide. Among sexually active adults aged 15-64 years old, 7.4% (95% CI, 6.7-8.2) were infected with HIV. Women were more likely to be infected (8.2%) than men (6.4%). Young women aged 15-24 years were nearly 5 times more likely to be infected (7.8%) than young men of the same age group (1.7%). HIV prevalence increased with age, with the highest prevalence (10.1%) between 30 and 39 years. Among 30-39 year olds, HIV prevalence was 11.0% among women compared to 9.0% among men. Prevalence among individuals aged 60-64 was 2.9%.

Although there was no difference in HIV prevalence between rural and urban areas, prevalence varied greatly across provinces (Figure 2.2). Women had higher HIV prevalence than men in all provinces. In Nyanza Province 17.7% (95% CI, 14.9-20.5) of women and 14.1% (95% CI, 11.4-16.9) of men were infected. HIV prevalence was higher among married or cohabiting (7.4%, 95% CI 6.6-8.2), separated/divorced (12.7%, 95% CI 9.1-16.2), and widowed individuals (21.3%, 95% CI 15.0-27.6) compared with never married individuals (4.3%, 95% CI 3.2-5.4). We observed no difference in HIV prevalence by wealth status for women and men; however, men who were currently employed had higher prevalence (6.8%, 95% CI 5.9-7.6) than those that were not employed (2.9%, 95% CI 1.0-4.8) (Table 2.1).

2.3.2 Behavioral factors and HIV infection

Among sexually active men, HIV prevalence was 18.1% (95% CI 14.8-21.4) among uncircumcised men and 4.5% (95% CI 3.8-5.2) among the circumcised men. HIV prevalence in uncircumcised men rose sharply between the 15-24 year age group (3.2%) and the 30-39 year age group (30.4%) and remained high in uncircumcised men through age 59.

Among participants who reported being sexually active in the last 12 months, consistent condom use with the last sex partner was associated with higher HIV prevalence compared to no condom use with the last sex partner (Table 2.1). However, a sub-analysis showed that HIV-infected persons who knew their sero-positive status were 4 times more likely to use a condom compared to those who self-reported an HIV negative status based on the result of their last test (53.1% vs. 13.9%) or those who had never had an HIV test (11.2%).

HIV prevalence also varied with STI infection. Respondents who reported any STI in the last 12 months had higher prevalence of HIV (16.5%) compared to those not reporting an STI (7.4%), and 44.7% of women and 32.0% of men were infected with HSV-2. HIV prevalence among those co-infected with HSV-2 was 15.6% compared to 2.3% among those not infected with HSV-2. Syphilis prevalence was 1.9% (1.6% and 2.3% among women and men, respectively). HIV prevalence was significantly higher among those infected with syphilis (16.5%) compared to those without syphilis infection (7.4%).
Table 2.1: HIV prevalence by demographic, behavioral and biologic factors among sexually active adults aged 15-64 years in Kenya in 2007

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<td>Active Syphilis infection***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis negative</td>
<td>6272</td>
<td>521</td>
<td>8.2 (7.3 - 9.2)</td>
<td>4962</td>
<td>301</td>
<td>6.2 (5.4 - 6.9)</td>
</tr>
<tr>
<td>Syphilis positive</td>
<td>106</td>
<td>13</td>
<td>11.8 (5.1 - 18.5)</td>
<td>107</td>
<td>20</td>
<td>18.6 (9.0 - 28.2)</td>
</tr>
<tr>
<td>STI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>154</td>
<td>28</td>
<td>17.0 (9.3 - 24.6)</td>
<td>135</td>
<td>17</td>
<td>15.9 (7.2 - 24.7)</td>
</tr>
<tr>
<td>No</td>
<td>5708</td>
<td>479</td>
<td>8.1 (7.2 - 9.1)</td>
<td>4670</td>
<td>297</td>
<td>6.4 (5.6 - 7.2)</td>
</tr>
</tbody>
</table>

**Widowhood**: Widowhood variable was defined as previous marriage that ended due to death of a spouse. Some previously widowed women had remarried when the survey was conducted.

**Mobility**: Mobility was defined as the number of separate occasions the respondent traveled away from home or community and slept away in the last 12 months.

**Active Syphilis infection***: Active syphilis infection was defined as positive RPR and TPPA serologies.
2.3.3 Factors independently associated with HIV

Women:

In multivariate analyses, independent correlates of HIV infection among sexually active women were geographical area of residence (Nyanza Province vs Nairobi: adjusted OR [AOR] 1.6, 95% CI 1.1-2.3), higher number of lifetime sex partners (6-9 vs 0-1 partners: AOR 3.0, 95% CI 1.6-5.9), HSV-2 infection (AOR 6.5, 95% CI 4.9-8.8), marital status (separated/divorced vs. never married: AOR 2.2, 95% CI 1.2-3.9; widowed vs. never married: AOR 2.7, 95% CI 1.5-4.8) and consistent condom use with the last sex partner (AOR 2.3, 95% CI 1.6-3.4) (Table 2.2).

Men:

Among men, correlates of HIV infection were age group (30-39 years vs. 15-24 years: AOR 5.2, 95% CI 2.6-10.5), number of lifetime sex partners (≥10 partners vs 0-1, AOR 3.5, 95% CI 1.4-9.0), HSV-2 infection (AOR 4.7 95% CI 3.2-6.8), syphilis infection (AOR 2.4, 95% CI 1.4-4.0), consistent condom use with the last sex partner (AOR 2.1, 95% CI 1.5-3.1) and lack of male circumcision (AOR 4.0, 95% CI 2.8 - 5.5) (Table 2.2).

2.3.4 Factors Associated with HIV in Nyanza Province:

Prevalence among sexually active adults in Nyanza province was highest in the 25-to-29-year-old age group for women (23.4%) and in the 30-to-39-year-old age group for men (25.9%). Of separated/divorced individuals, 42.2% were HIV-infected; uncircumcised men had a prevalence of 20.8% compared to the 6.8% among those circumcised. In multivariate analysis, factors independently associated with HIV prevalence among recently sexually active women were age group 25-29 years vs.
15-24 years (AOR 1.3, 95% CI 0.8-2.3); current marital status (separated/divorced vs. never married: AOR 5.7, 95% CI 1.5-20.9; widowed vs. never married: AOR 4.4, 95% CI 1.0-19.5), HSV-2 infection (AOR 6.4, 95% CI 3.6-11.4), higher number of lifetime sex partners (6-9 vs 0-1: AOR 3.2, 95% CI 1.2-9.0), consistent condom use with the last sex partner (AOR 3.2, 95% CI 1.9-5.5), mobility (2 days vs. 0 days: AOR 1.4, 95% CI 0.9-2.3). Factors associated with HIV infection among recently sexually active men were age group 30-39 years vs. 15-24 years (AOR 19.1, 95% CI 5.9-61.6); education (incomplete primary vs. no primary: AOR 1.4, 95% CI 0.5-4.0), HSV-2 infection (AOR 4.6, 95% CI 2.2-9.4), consistent condom use with the last sex partner (AOR 3.7, 95% CI 2.0-7.1), and lack of male circumcision among men (AOR 2.8, 95% CI 1.7-4.8).

Table 2.2: Factors independently associated with HIV infection among sexually active adults in Kenya in 2007.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted odds ratio (95% confidence interval)</td>
<td>Adjusted odds ratio (95% confidence interval)</td>
</tr>
<tr>
<td>Province</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nairobi</td>
<td>ref</td>
<td>-</td>
</tr>
<tr>
<td>Central</td>
<td>0.4(0.3 - 0.8)</td>
<td>-</td>
</tr>
<tr>
<td>Coast</td>
<td>0.8(0.5 - 1.3)</td>
<td>-</td>
</tr>
<tr>
<td>Eastern</td>
<td>0.7(0.4 - 1.1)</td>
<td>-</td>
</tr>
<tr>
<td>North-Eastern</td>
<td>0.4(0.1 - 1.2)</td>
<td>-</td>
</tr>
<tr>
<td>Nyanza</td>
<td>1.6(1.1 - 2.3)</td>
<td>-</td>
</tr>
<tr>
<td>Rift-Valley</td>
<td>0.7(0.4 - 1.1)</td>
<td>-</td>
</tr>
<tr>
<td>Western</td>
<td>0.6(0.3 - 0.9)</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>25-29</td>
<td>1.2(0.9 - 1.7)</td>
<td>4.3(2.1 - 9.1)</td>
</tr>
<tr>
<td>30-39</td>
<td>1.1(0.8 - 1.5)</td>
<td>5.2(2.6 - 10.5)</td>
</tr>
<tr>
<td>40-49</td>
<td>0.4(0.3 - 0.6)</td>
<td>3.1(1.4 - 6.6)</td>
</tr>
<tr>
<td>50-59</td>
<td>0.3(0.1 - 0.5)</td>
<td>1.9(0.8 - 4.4)</td>
</tr>
<tr>
<td>60-64</td>
<td>0.6(0.1 - 2.3)</td>
<td>1.2(0.4 - 3.6)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married/cohabitating</td>
<td>ref</td>
<td>-</td>
</tr>
<tr>
<td>Currently married/cohabitating</td>
<td>1.5(0.9 - 2.4)</td>
<td>-</td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>2.2(1.2 - 3.9)</td>
<td>-</td>
</tr>
<tr>
<td>Widowed</td>
<td>2.7(1.5 - 4.8)</td>
<td>-</td>
</tr>
<tr>
<td>HSV-2 infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-2 negative</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>HSV-2 positive</td>
<td>6.5(4.9 - 8.8)</td>
<td>4.7(3.2 - 6.8)</td>
</tr>
<tr>
<td>Circumcision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>-</td>
<td>Ref</td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>4.0(2.8 - 5.5)</td>
</tr>
</tbody>
</table>
### 2.4 Discussion

In 2007, an estimated 7.4% of sexually active Kenyan adults aged 15-64 years were infected with HIV. Correlates of HIV infection among women and men were age, number of lifetime sex partners, residence in Nyanza province, HSV-2 infection, consistent condom use with the last sex partner and lack of circumcision among men. The strongest independent predictors for HIV infection for both women and men were HSV-2 co-infection and higher number of lifetime sex partners.

HIV prevalence was highest in Nyanza Province, where 16.9% of the sexually active adults were HIV-infected. In a sub-analysis for Nyanza Province, we found that age, HSV-2 infection, multiple lifetime sex partners, consistent condom use with the last sex partner and lack of male circumcision were independently associated with HIV. Many of these factors are similar to predictors of HIV infection found at the national level and are consistent with findings from other studies (1;8;16;19).

In Kenya, the adjusted odds of having HIV among sexually active persons with HSV-2 infection were 5-6-fold higher than those uninfected with HSV-2. However, awareness of HSV-2 is very low, even among health care providers, despite the high prevalence of HSV-2 and the potential role of HSV-2 in driving the HIV epidemic (20;21). HIV-induced immune compromise can result in frequent and persistent HSV disease, while poorly managed HSV replication may influence HIV transmission (22). Researchers estimate that in settings with high HSV-2 prevalence, such as

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### Table 1: Adjusted odds ratios (95% confidence interval) of HIV infection by lifetime sexual partners and condom use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime sexual partners</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>10+</td>
<td>2.4(1.0 - 5.8)</td>
<td>3.5(1.4 - 9.0)</td>
</tr>
<tr>
<td>2-3</td>
<td>1.5(1.1 - 2.1)</td>
<td>2.0(0.8 - 4.8)</td>
</tr>
<tr>
<td>4-5</td>
<td>2.3(1.6 - 3.5)</td>
<td>2.2(0.8 - 5.8)</td>
</tr>
<tr>
<td>6-9</td>
<td>3.0(1.6 - 5.9)</td>
<td>2.6(1.0 - 6.9)</td>
</tr>
<tr>
<td>Consistent condom use with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>last sex partner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.3(1.6 - 3.4)</td>
<td>2.1(1.5 - 3.1)</td>
</tr>
</tbody>
</table>

---

* Active Syphilis infection: Active syphilis infection was defined as positive RPR and TPPA serologies.
Nyanza province, HSV-2 infection could contribute to the risk of HIV-infection in more than one in four new cases of HIV (19;21). Unfortunately, randomized controlled trials that have examined daily acyclovir treatment of HSV-2 among persons with HIV co-infection, or acyclovir prophylaxis among persons without HIV have not demonstrated a protective effect (23).

The results from KAIS show a non-statistically significant increase in overall HIV prevalence from KDHS 2003 (7.4% vs. 6.7%) among those aged 15-49. The potential increase in HIV prevalence may be in part due to the survival effects of antiretroviral therapy. It may also indicate increasing incidence and a need to improve and expand HIV prevention programs throughout Kenya, and particularly in Nyanza Province. Appropriate messages on delaying sexual debut, knowledge of HIV status, male circumcision, consistent and correct use of condom with partner of unknown HIV status or known discordant HIV status, and reduction of number of sex partners should be reinforced (8;24;25). Our study showed that widowhood and divorce were significantly associated with higher HIV prevalence. This corroborates findings from other sub-Saharan African countries which show that women who encounter marital disruption through divorce or widowhood were more likely to be HIV infected (26). On the other hand, divorce is more common among HIV-infected women, particularly those in HIV discordant unions (27).

Ethnicity and province influence both the distribution of circumcision practice and HIV prevalence. Several studies have showed that male circumcision reduces the risk of HIV acquisition among men [28]. High prevalence in Nyanza province could be attributed to low male circumcision rates. Among the general population, 85% of men were circumcised nationally while 48.2% were circumcised in Nyanza Province. In addition, cultural practices such as widow inheritance practiced among the Luo community (the predominant ethnic group in Nyanza) may be a factor (28;29). A study by Agot et al (30) in Nyanza province showed that inherited widows (defined as a woman over whom a designated male has assumed social and economic responsibility, following the death of a husband (30)) were more likely to have HIV infection compared to those not inherited. Luo women are believed to acquire contagious cultural impurity following the death of a husband. Often, a professional “cleanser” is hired who performs sexual rituals to cleanse the widow. If the spouse of the deceased is HIV-infected, the cleanser acts as a bridge for HIV transmission to other widows hence putting widowed women at a high risk (31).

The Kenya Ministries of Health published The National Guidance for Voluntary Medical Male Circumcision (VMMC) in January 2008 and in November 2008 launched the VMMC program focusing on Nyanza province and other traditionally non-circumcising communities with the aim of reducing new HIV infections and other STIs. The guidance provides a broad policy framework for the integration of VMMC into existing HIV prevention programs.

Respondents reporting ever having used condoms were more likely to have HIV infection. Condom use reduces risk of HIV acquisition and transmission (32) and HIV-infected persons who are aware of their HIV infection are more likely to use condoms (33;34). KAIS showed a 4-fold increase in condom use among those who knew their HIV-positive status. Though the association between condom use and HIV infection was not expected, the finding may reflect the success of positive prevention interventions and condom promotion efforts to increase condom use by people living with HIV. These data highlight the need for future HIV surveys to collect more detailed partner-specific information on condom use and knowledge of HIV status of participants and their partners which could help interpret the complex associations between condom use, sexual behavior, and HIV. The application of a laboratory assay that can accurately distinguish recent from established infection could also suggest the temporality of any associations between HIV infection and condom use, and more accurately highlight areas for programmatic focus.
Our study was limited by several factors. About 20% of eligible residents were either not present or declined to participate in the interview and blood draw. Although we do not expect that there is significant participation bias, we were not able to conduct these analyses; however, appropriate weighting was applied to adjust for non-response. These results cannot be generalized to all Kenyans, but only to those that reported recent sexual activity. Additionally, key sexual behavior indicators were based on self-reported data. Though KAIS interviewers were trained on asking sensitive questions around sexual behavior and ensuring respondent confidentiality, there is a possibility that these questions were not accurately answered. We did not ask how long after circumcision the men engaged in sexual intercourse. The cross-sectional design of the study limited our interpretation of the temporality of association between the factors examined and HIV infection. The survey also did not ask questions on men having sex with men or injecting drug use activities that are practiced in Kenya and may contribute to new HIV infections (13). We did not include children due to the relatively low HIV prevalence among this group.

HIV remains a major public health challenge in Kenya. Although various prevention, care and treatment programs have been initiated and expanded in Kenya, evidence based prevention efforts that target known behavioral and biologic factors such as reduction of sex partners, condom use, delayed sexual debut and male circumcision should be enhanced. The wide regional variation in HIV prevalence reinforces the need for targeted prevention interventions focusing on provinces with high infection rates, while at the same time addressing the key behavioral factors that are associated with the risk of HIV infection nationally.

Acknowledgements

Special thanks to Professor George Rutherford of the University of California, San Francisco, for his useful comments and assistance in editing this paper.
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Chapter 3

Better adherence to pre-Antiretroviral Therapy guideline after implementing an Electronic Medical Record system in Rural Kenyan HIV clinics: a multi-center pre-post study


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Victor Ssem pijja
Abraham Katana
Patrick Langat
Nicky Okeyo
Ameen Abu-Hanna
Nicolette de Keizer
Co-authors’ contribution

T. Oluoch, A. Abu-Hanna and N. de Keizer conceptualized and designed the study. A. Katana and D. Kvaro reviewed the clinical components of the study and manuscript. V. Ssempijja was the study statistician and developed the analysis programs. P. Langat and N. Okeyo provided oversight to the data management team that conducted the data collection, de-identification and cleaning. All co-authors were involved in interpreting the results. T. Oluoch and N. de Keizer drafted and revised the manuscript. All authors edited and reviewed the manuscript and gave their final approval for submission to the journal.
Abstract

Introduction:
Monitoring pre-antiretroviral therapy (pre-ART) care is key quality of HIV care indicator. This study investigates how the use of EMR is associated with adherence to pre-ART guidelines in rural HIV clinics in Kenya.

Methods:
A retrospective study to compare quality of pre-ART care using three indicators: (a) performing baseline CD4 test, (b) time from enrollment to care to first CD4 test, (c) time from baseline CD4 to second CD4 test; pre and post introduction of an EMR system at 17 rural HIV clinics.

Results:
A total of 18,523 patients were receiving pre-ART care of whom 38.8% in the paper group had at least one CD4 test compared to 53.4% in the EMR group (p<0.001). The adjusted odds of performing a CD4 test in clinics using an EMR was 1.59 (95% CI: 1.49 – 1.69). Median time from enrolment into HIV care to first CD4 test was 1.40 months (IQR: 0.47 – 4.87) for paper versus 0.93 months (IQR: 0.43 – 3.37) for EMR. Median time from baseline to first CD4 follow-up was 7.5 months (IQR: 5.97 – 10.73) for paper and 6.53 months (IQR 5.57 – 7.87) for EMR.

Conclusion:
Use of EMRs was associated with better compliance to HIV guidelines for pre-ART care. EMRs potentially have a positive impact on quality of care for HIV patients in resource-constrained settings.
3.1 Introduction

Nearly two-thirds of the 34 million persons infected with HIV globally live in sub-Saharan Africa (SSA) (1). As of December 2011, 70% of the 1.7 million HIV-related deaths occurred in SSA (2). The high volume of patients in an environment that lacks adequate skilled human resources and equipment, adds to the dire need to invent ways to improve the quality of care for those infected with HIV. Despite the availability of diagnostic testing for HIV and the availability of highly active antiretroviral therapy (ART) since the mid 1990’s, early mortality remains high among patients who access ART with advanced symptomatic disease and low baseline CD4 (3;4). Effective pre-ART patient monitoring and timely initiation of ART can potentially reduce HIV-related mortality (5). The 2010 revision of the WHO guidelines on ART for HIV infection recommends using CD4 cell counts to monitor pre-ART care and determine patient eligibility for ART initiation (6). Although the 2013 revision of the WHO guidelines recommending the use of viral load for patient monitoring were released in July 2013 (7), many countries are yet to adapt them.

Various studies have shown the benefits of electronic medical record (EMR) systems in delivery of quality health care for chronic illnesses (8-10). EMRs can be integrated into clinical practice to enhance guideline adherence. Despite the evidence of the benefits of EMRs, many health facilities that offer HIV care and treatment in sub-Saharan Africa use paper-based records for patient data (11). As the number of enrolled patients increases against a relatively fixed number of overworked health workers, the paper records become more prone to error, less efficient and ineffective in managing the complex longitudinal patient data. This situation can potentially compromise the quality of information used for patient care and thereby negatively affect patient outcomes. Due to these considerations, a number of health facilities in SSA are transitioning practice from use of paper to EMRs in order to improve patient monitoring and hence quality of care (10).

The Kenyan Ministries of Health (MOH) and the US President’s Emergency Plan for AIDS Relief (PEPFAR) have provided resources for the national rollout of EMRs at HIV, tuberculosis and maternal and child health (MCH) clinics to improve data management for clinical decision making and reporting. The aim of this study was to assess the effect of change from a paper-based to an electronic-based medical record system on CD4 testing among HIV-infected persons in the pre-ART care period.

3.2 Methods

We conducted a retrospective study to compare quality of care indicators before and after the introduction of an EMR system at 17 health facilities providing HIV care and treatment services in Nyanza province, western Kenya. Study participants were patients aged 2 years or older receiving HIV care at the participating clinics since the Kenya HIV guidelines require that all children below the age of 2 years should initiate ART irrespective of their immunological status. All the clinics had used paper-based records before transitioning to electronic records at varying times from January 2009 to February 2012.

3.2.1 Study setting

Nyanza province has the highest HIV burden among Kenya’s eight provinces with a prevalence of 14.9% and is home to about a third of all HIV-infected persons in Kenya (12). EMRs were installed at 17 health facilities that had electricity and adequate security for computers. The 17 clinics, which were providing HIV care and treatment to about 39,203 active patients as of September 2012(13), are all located in rural
settings and encounter common challenges including inadequate staffing and weak infrastructure, which includes frequent electric power interruptions and unreliable Internet access. The studied facilities fall into three categories established by the Government of Kenya, namely: district hospitals (n=4) – level 4 (these headed by a physician and provide both inpatient and outpatient services), health centers (n=11) – level 3 (these are headed by a clinical officer who is equivalent to a physician assistant; they provide a limited number of services compared to district hospitals), and dispensaries (n=2) – level 2 (these are headed by a nurse and provide only limited outpatient services).

3.2.2 Pre-ART care

Pre-ART care is provided during the period between a confirmed HIV-positive test and eligibility for ART initiation based on Kenyan ART guidelines. Pre-ART care is offered at no cost to patients in many SSA countries. During the pre-ART care period, HIV-infected patients receive a range of clinical services which include provision of cotrimoxazole prophylaxis, multivitamins, screening for TB and other opportunistic infections, and routine laboratory monitoring – key among them being CD4 cell count every 6 months and viral load tests. CD4 cell count serves as the most important laboratory indicator of the degree of immunosuppression among HIV patients and most important prognosis indicator for patients starting ART (3;4;14). The CD4 test is now widely available in health facilities in sub-Saharan Africa for routinely monitoring HIV disease progression and response to treatment.

3.2.3 Paper-based patient monitoring system

The paper-based system entailed recording of patient details on an MOH-approved Comprehensive Care Clinic Card (MOH 257) (Appendix 3.1). The MOH 257 contained demographic and contact details of the patient, treatment support data, HIV testing and treatment history, allergies, HIV treatment eligibility and regimen (first or second line), vital signs, treatment outcomes, laboratory results including CD4, co-infections and an appointment date for the next visit. Observations for each visit are recorded on a single column of a paper-chart, see Appendix 3.1.

Scheduling patient visits for each clinic day was done manually from the MOH 257 where the follow-up visit date was recorded. Analyses such as tracking of patient clinic visit appointments, trends in measurements such as vital signs and treatment progress including CD4 cell counts, statistical summaries for hospital administration use and MOH reporting were all conducted manually. Clinicians review individual patient’s treatment history based on filed paper notes during routine clinic visits.

3.2.4 Electronic Medical Record (EMR) System

The EMR system rolled-out in the 17 facilities is called Comprehensive Care Centre Patient Application Database (C-PAD) and was developed in 2007. Data management entails clinicians recording information on paper forms (MOH 257), as was the case for the paper-based system, followed by data entry by a data clerk into the EMR on the same or next day after the clinic visit. Mandatory variables such as demographic data, vital signs, medication and key laboratory measurements must be entered into the computer for the continuation of system operation. It takes about 10 minutes to enter the records of a new patient and about 5 minutes to update the records of a revisit patient if all required information is available. Data clerks make immediate follow-up with the clinicians to provide any missing data. Weekly reviews of EMR-generated patient summary reports are used to flag patients with conditions that need follow-up – for example, patients with no baseline CD4 result or those whose follow-up CD4 tests are overdue. Data entry by data clerks is common practice in many SSA countries as clinics transition from...
use of paper to electronic systems. Clinicians interact with the EMRs through the weekly patient summary reports or by directly reviewing individual patient data on the EMR in addition to the paper records.

For this study, pre-EMR data from the paper forms (MOH 257) were entered retrospectively for all patients who initiated treatment prior to the EMR system installation, and compared to electronic data for patients enrolled in HIV care after the installation of the EMR.

### 3.2.5 Outcome measures

We assessed the effect of EMR use on the following factors that are key in pre-ART care:

a) Performing a baseline CD4 test,

b) Time from enrolment into HIV care to the first (baseline) CD4 testing,

c) Time from first to second CD4 test

Each patient enrolled in HIV care should get a baseline CD4 test (a), the shorter the time from enrolment into HIV care to baseline CD4 (b), the better the compliance with HIV treatment guidelines (14).

According to the HIV treatment guidelines, a repeat CD4 test should be performed for every patient at least once every 6 months (c). For each site the date of C-PAD installation was used to compare the outcome measures during the paper-based versus the EMR-based data management.

### 3.2.6 Statistical Analysis

Data for each visit are ordered by visit date and records with a CD4 count but with no CD4 date, had the CD4 date imputed using the clinic appointment date prior to that corresponding to the CD4 result in the database. We used descriptive statistics to summarize continuous variables using median and inter-quartile range (IQR). Logistic regression was used to calculate Odd Ratios (OR), adjusted Odds Ratios (aOR) to test for association between EMR use and performing baseline CD4 test. Cox proportional hazards regression was used to calculate Hazard Ratios (HR), adjusted Hazard Ratios (aHR) to test the associations between EMR use and the time-based outcomes (time from enrolment on HIV care to first CD4 test and time from first to second CD4 tests). In multivariate analyses (Cox proportional hazard and logistic regression), we adjusted for age and sex of patient, year of change of treatment guidelines and the level of the health facility, and used paper system as the reference group. Kaplan-Meier survival graphs were used to visually present the comparison of time to event, for the two time-based outcomes. For time-based outcomes, records that did not have a CD4 test result were censored on the date of last visit. The log rank test of equality was used to test for statistical difference in the rate of occurrence of the time-based outcomes in the paper and EMR groups. The survivor function measurement was used to calculate median time to event and the Inter-Quartile Range (IQR). Pearson’s Chi-square test was used to compare proportions and to calculate associated p-values. Generalized estimating equations (GEE) method was used to adjust for intra-facility correlation. Statistical analysis was conducted using Stata version 12.1.

### 3.2.7 Ethical Considerations

The study was approved by the US Centers for Disease Control and Prevention (CDC) and KEMRI institutional review boards. Individual patient data were de-identified by the KEMRI staff responsible for primary data collection prior to analysis.
3.3 Results

A total of 37,851 patients aged 2 years or older were enrolled at the clinics, of which 18,523 (48.9%) were receiving pre-ART care as they were not yet eligible for ART based on the national guidelines. This excluded 2,414 patients who had transferred in from other clinics. The pre-ART care patients consisted of 12,529 females (67%) and 5,994 males (33%). Overall, 15,476 patients were enrolled on HIV care before the implementation of the EMR (paper group) while 3,047 were enrolled after the EMR implementation (EMR group). Median age of patients at enrolment in the paper and EMRs groups were 28.9 years (IQR: 22.8 – 37.2) and 28.1 years (IQR: 23.0 – 35.9) respectively. Table 3.1 shows the characteristics of the Pre-ART patients.

Table 3.1: Characteristics of Pre-ART patients receiving HIV care during the paper and EMR phases at 17 health facilities in Siaya County, Western Kenya.

<table>
<thead>
<tr>
<th></th>
<th>Paper: n (%)</th>
<th>EMR: n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients (N)</strong></td>
<td>15,476</td>
<td>3,047</td>
<td>18,523</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4938 (31.9%)</td>
<td>1056 (34.7%)</td>
<td>5994</td>
</tr>
<tr>
<td>Female</td>
<td>10538 (68.1%)</td>
<td>1991 (65.3%)</td>
<td>12529</td>
</tr>
<tr>
<td><strong>Median Age (years)</strong></td>
<td>28.9</td>
<td>28.1</td>
<td>28.7</td>
</tr>
<tr>
<td><strong>WHO Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4408 (29.9%)</td>
<td>1239 (46.3%)</td>
<td>5647</td>
</tr>
<tr>
<td>2</td>
<td>4197 (28.5%)</td>
<td>852 (31.8%)</td>
<td>5049</td>
</tr>
<tr>
<td>3</td>
<td>5763 (39.1%)</td>
<td>527 (19.7%)</td>
<td>6290</td>
</tr>
<tr>
<td>4</td>
<td>371 (2.5%)</td>
<td>58 (2.2%)</td>
<td>429</td>
</tr>
<tr>
<td><strong>Recorded CD4 results</strong></td>
<td>6,001 (38.8%)</td>
<td>1,626 (53.4%)</td>
<td>7,627 (41.2%)</td>
</tr>
<tr>
<td><strong>MOH Level (Clinic type)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>664 (4.3%)</td>
<td>98 (3.2%)</td>
<td>762</td>
</tr>
<tr>
<td>3</td>
<td>2799 (18.1%)</td>
<td>460 (15.1%)</td>
<td>3259</td>
</tr>
<tr>
<td>4</td>
<td>12013 (77.6%)</td>
<td>2483 (81.7%)</td>
<td>14502</td>
</tr>
<tr>
<td><strong>Mean Duration of data collection (months)</strong></td>
<td>55.3</td>
<td>14.1</td>
<td>35.2</td>
</tr>
</tbody>
</table>
3.3.1 Association between EMR use and performing baseline CD4 test

Among the 18,523 patients receiving pre-ART care, 7,627 (41.2%) had at least one CD4 test result recorded while 10,896 (59%) did not have any CD4 test results. Among the pre-ART care patients, 6,001 (38.8%) in the paper group had at least one CD4 test while 1,626 (53.4%) in the EMR group had at least one CD4 test. These included 15.7% (n=1,195) and 9.2% (n=150) of patients with imputed CD4 test dates in the paper and EMR groups respectively (patients who had a CD4 result recorded but missing the date of CD4 test). In bivariate analysis, the odds of performing the baseline CD4 test was 57 percent higher using an EMR compared to the paper system OR = 1.57 (95% CI: 1.49 – 1.66). After adjusting for patient age and sex, level of health facility and year of change of treatment guidelines, the use of EMR was independently associated with an 59% higher odds of ever performing the baseline CD4 test compared to paper system (adjusted Odds Ratio – aOR: 1.59, 95% CI: 1.49 – 1.69).

3.3.2 Time from enrolment into HIV care to the first CD4 testing among pre-ART patients

Among the pre-ART patients who had at least one CD4 test, the median time from enrolment into HIV care to first CD4 test was 1.40 months (IQR: 0.47 – 4.87) for paper versus 0.93 months (IQR: 0.43 – 3.37) for EMR. Figure 3.1 shows the time from enrolment on HIV care to baseline CD4 test. The proportion of patients with baseline CD4 tests conducted within 3 months of enrolment was 64.8% (95% CI: 63.1 – 66.5) for the paper-based system versus 74.1% (95% CI: 70.5 – 77.5) for the EMR system. The unadjusted analysis using Cox regression indicated that EMR use was associated with a 57% higher hazard of conducting a CD4 test compared to the paper system HR = 1.57 (95% CI: 1.26 – 1.95). After adjusting for age and sex of the patient, level of health facility and year of change of treatment guidelines, EMR use was associated with a hazard ratio of 1.49% (95% CI: 1.17 – 1.88).

3.3.3 Time from first CD4 test to second CD4 test among pre-ART patients

Among the 18,523 pre-ART patients, 2,863 (15.5%) had had at least two CD4 tests done; 2,295 (14.8%) were in the paper group while 568 (18.6%) were in the EMR group. The median time from baseline to first follow-up CD4 was 7.5 months (IQR: 5.97 – 10.73) for paper and 6.53 months (IQR 5.57 – 7.87) for EMR. Figure 3.2 shows the Kaplan-Meier curves for the time from first to second CD4 test. Six months after the first CD4 test, 25.7% (95% CI: 24.0 – 27.5) of patients had had a second CD4 test for paper-based system compared to 35.0% (95% CI: 31.2 – 39.1) using EMR system. The hazard ratio of conducting a second CD4 test was 1.78 (95% CI: 1.30 – 2.46). After adjusting for patient age and sex, level of health facility and year of change of treatment guidelines, EMR use was associated with a 49% higher hazard of conducting a second CD4 test (aHR: 2.09 (95% CI: 1.41 – 3.09)).

Among the patients enrolled on pre-ART HIV care, 1,591 (8.6%) and 914 (4.9%) had at least three and four CD4 tests respectively. The intervals between the successive tests were comparable to the time from first to second CD4 tests.
Figure 3.1: Time from enrolment into HIV care to first CD4 test among pre-ART patients in Siaya County, western Kenya.

Figure 3.2: Time from first to second CD4 test among pre-ART HIV care patients in Siaya County, western Kenya.
3.4 Discussion

EMR use was associated with better adherence to the pre-ART care guidelines in all of the 3 outcome measures. The clinical guidelines (14) require that baseline CD4 test be conducted at enrolment; however, only 41% of the patients had a baseline CD4 recorded. Among those with a recorded baseline CD4, two-thirds of patients on paper system and three-quarters on EMRs had a baseline CD4 test three months after enrolment into pre-ART care. EMRs were associated with a 59% increase in the odds of performing a baseline CD4 test. There was a significant reduction in time from enrolment into pre-ART care to the first CD4. EMR use was associated with a 47% higher hazard of conducting a baseline CD4 test. The proportion of patients who had had a second CD4 test 6 months after the first one was low. Only 26% (paper) and 35% (EMR) of patients had a second CD4 at 6 months as required in the ART guidelines. The median time from first to second CD4 test using EMR was closer to the recommended six months compared to paper system.

Although not reported in the results section, we found data quality to be better in the EMR compared to the paper system. For example, key data elements such as date of CD4, CD4 results were three times more likely to be missing on paper system compared to EMRs. This could be attributed to the fact that the EMR contains mandatory fields that must be entered, resulting in fewer missing values. Data clerks also add a layer of data quality checks during data entry into the EMR and consult with clinicians when they encounter missing values. In some cases, results are lost between the lab and the data entry room. In such cases, even an EMR was not able to improve the completeness of recorded data and this could have contributed to the missing CD4 results as reported on this paper. Some CD4 tests, mainly in the EMR group, were conducted earlier than the 6 months stipulated in the guidelines. An earlier CD4 test can be ordered if a clinician suspects HIV treatment failure or if a previous CD4 test was conducted when a patient had an acute illness.

The findings of our study are consistent with studies by Williams, Were and Alamo which were also conducted in resource-constrained settings (10;15;16). These studies showed that EMR use was associated with reduction in time to various events such as patient waiting time, time spent by clinicians attending to patients and time to order a laboratory test in HIV clinics. The three studies above were each conducted in a single clinic, with a relatively small sample size compared to our study.

One of the key strengths of the study is that the data were collected from 17 clinics thereby providing a large and general patient population. All the clinics use the same guidelines (14) and the same EMR hence the patient management procedures, administrative procedures, drug regimens and laboratory investigations are standardized.

Our study was limited by some factors. EMRs are still not fully used at the point of care mainly due to infrastructural problems such as lack of reliable electric power. The clinics have however made every effort to ensure that the time between the consultation and the entry of the records into the computer is as short as possible so that clinical staff can provide any missing data or act on incorrect data promptly. We also dropped records that did not have an enrolment date recorded and imputed CD4 dates in cases where CD4 results were recorded but the CD4 test date was missing. Nearly 60% of the patients did not have a CD4 test result recorded. This was due to a combination of data quality problems, missed orders and missing or lost results from the laboratory. Other contributing factors could be limited access to CD4 tests in rural areas, where the study sites are located, equipment breakdown, stock outs of test reagents, inadequate staff in the lab and the clinicians being unaware of the guidelines. Due to the retrospective nature of our study we are not able to pinpoint the contribution of each of the aforementioned reasons for missing CD4 test results. We were also unable to quantify the
fraction of missing data that required additional consultation between the data clerk and clinician. However, the data clerks and clinicians indicated that the missing information that required consultations reduced with time. Additionally, the retrospective observational, before-and-after design of this study we are not able to determine a cause-effect relation between the use of EMR and the outcome variables. Some of the outcomes could have been effected temporal changes such as improved practice, delivery of supplies and improved laboratory equipment. Further investigation on the strength of associations between EMR and the outcomes described in this study needs to be assessed through a prospective randomized controlled trial.

3.4.1 Implications of the study

EMRs seem to improve quality of patient care. As many health care systems in the developing countries increase investments in these technologies in order to provide quality care to the increasing volumes of HIV patients, there is need for the quantification of empirical evidence of the impact of such interventions on quality of care. In a competitive funding environment, only technologies that have been shown to be positively associated with adherence to guidelines and better quality of care justify funding. This study therefore adds to the body of knowledge that will inform deployment of EMRs in resource-limited settings like Kenya. Additionally, the data presented in this study shows that there is need to improve the timeliness of conducting CD4 tests.

Further work on the evaluation of use of clinical decision support functionality of an EMR on compliance with pre-ART guidelines is needed to provide a more complete picture of the effect of EMRs. Specifically, there is need to assess whether the benefits of point of care use of EMRs with decision support system in resource-limited settings can be similar to those documented in developed countries (17;18).

3.5 Conclusion

Our study demonstrated that use of EMRs is positively associated with enhanced compliance with key quality indicators for pre-ART care as required by the HIV treatment guidelines. EMRs potentially have a positive impact on quality of care for HIV patients in resource constrained setting. However, there still is need for much greater improvements.
Reference List

(8) Bell DS, Cima L, Seiden DS, Nakazono TT, Alcouloumre MS, Cunningham WE. Effects of laboratory data exchange in the care of patients with HIV. Int J Med Inform 2012 Aug 17.
Appendix 3.1: MOH 257 – Comprehensive Care Clinic Patient Card

**COMPREHENSIVE CARE CLINIC PATIENT CARD**

**DEMOGRAPHIC CHARACTERISTICS:**

- **Unique Patient Number:** _______________________
- **MOH 257**

**ART THERAPY:**

- **Date medically eligible:**
- **WHO clinical stage:**
- **Reason for eligibility:**
  - CD4%: Clinical only
  - ILC
- **Date eligible and ready for ART:**
- **Transfer in with Records:**
- **Date from:**
  - **Name of District:**
  - **Name of Facility:**
  - **Determined ART:**

**COHORT:**

- **Month:**
- **Year:**

**Data entered on 1st line initial regimen:**

- **Regimen:**
- **At start of ART:**
  - **Weight (Kgs):**
  - **Function status:**
  - **WHO Clinical stage:**

**Substitution of ARVs within first line regimen:**

<table>
<thead>
<tr>
<th>Date</th>
<th>New Regimen</th>
<th>Reason for substitute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Date switched to 2nd line regimen:**

<table>
<thead>
<tr>
<th>Date</th>
<th>New Regimen</th>
<th>Reason for substitute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

**Substitution of ARVs within 2nd line regimen:**

<table>
<thead>
<tr>
<th>Date</th>
<th>New Regimen</th>
<th>Reason for substitute</th>
</tr>
</thead>
<tbody>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Date patient transferred out:** _______________________

**ART treatment interruptions:**

<table>
<thead>
<tr>
<th>Stop/Loss/Dead (Circle appropriate)</th>
<th>Date</th>
<th>Reason's for STOP</th>
<th>Date Restarted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop/Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop/Death</td>
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<td></td>
<td></td>
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<tr>
<td>Stop/Death</td>
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<tr>
<td>Stop/Death</td>
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<td></td>
</tr>
<tr>
<td>Stop/Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop/Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ART HISTORY:**

- **Transfer in with records:**
- **Earlier ARV but not a transfer in:**
- **PMCT only:**
- **None:**

**Date patient HIV test confirmed:**

- **Date enrolled in HIV care clinic:**
- **Date PEP offered:**
- **Reason for PEP:**

**KNOWN DRUG ALLERGIES:**
<table>
<thead>
<tr>
<th>Date (Tick if visit is scheduled/If patient is ill write pick up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up date</td>
</tr>
<tr>
<td>Duration in month since start of ART</td>
</tr>
<tr>
<td>Weight (Kgs)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>If Pregnant, EDD/PROM?</td>
</tr>
<tr>
<td>FP / NO FP</td>
</tr>
<tr>
<td>IF FP, Method?</td>
</tr>
<tr>
<td>IF CHILD, HEIGHT</td>
</tr>
<tr>
<td>Function: W, A, B</td>
</tr>
<tr>
<td>WHO clinical stage</td>
</tr>
<tr>
<td>TB Status</td>
</tr>
<tr>
<td>Potential Side effects</td>
</tr>
<tr>
<td>New OI, Other Problems</td>
</tr>
<tr>
<td>Cotrimoxazole, Adherence, Dose</td>
</tr>
<tr>
<td>Other medications dispensed</td>
</tr>
<tr>
<td>Adherence? WHY?</td>
</tr>
<tr>
<td>ARV drugs</td>
</tr>
<tr>
<td>Regimen/Dose dispensed</td>
</tr>
<tr>
<td>CD4/%, Results/ Date</td>
</tr>
<tr>
<td>Hb, TLC, HEP, B, other lab tests</td>
</tr>
<tr>
<td>Referred To?</td>
</tr>
<tr>
<td>If hospitalized, No. of days</td>
</tr>
<tr>
<td>Clinicians initials</td>
</tr>
</tbody>
</table>

Yellow highlights show the variables abstracted from the patient data.
Chapter 4

Electronic Medical Record systems are associated with appropriate placement of HIV patients on ART in rural health facilities in Kenya: A retrospective pre-post study

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Co-authors’ contribution

T. Oluoch, A. Abu-Hanna and N. de Keizer conceptualized and designed the study. A. Katana, D. Kwaro and D. Kimanga reviewed the clinical components of the study and manuscript. V. Ssempijja was the study statistician and developed the analysis programs. P. Langat and N. Okeyo provided oversight to the data management team that conducted the data collection, de-identification and cleaning. All co-authors were involved in interpreting the results. T. Oluoch and N. de Keizer drafted and revised the manuscript. All authors edited and reviewed the manuscript and gave their final approval for submission to the journal.
Abstract

Introduction:
There is little evidence that EMR use is associated with better compliance with clinical guidelines on initiation of ART among ART-eligible HIV patients. We assessed the effect of transitioning from paper-based to an EMR-based system on appropriate placement on ART among eligible patients.

Methods:
We conducted a retrospective, pre-post EMR study among patients enrolled in HIV care and eligible for ART at 17 rural Kenyan clinics and compared the: (1) Proportion of patients eligible for ART based on CD4+ count or WHO staging who initiate therapy; (2) Time from eligibility for ART to ART initiation; (3) Time from ART initiation to first CD4 test.

Results:
A total of 7,298 patients were eligible for ART; 54.8% (n=3,998) were enrolled in HIV care using paper-based system while 45.2% (n=3,300) were enrolled after the implementation of the EMR. EMR was independently associated with a 22% increase in the odds of initiating ART among eligible patients (adjusted Odds Ratio (aOR) 1.22, 95% CI: 1.12 – 1.33). The proportion of ART eligible patients not receiving ART was 20.3% and 15.1% for paper and EMR, respectively (χ² = 33.5 and p<0.01). Median time from ART eligibility to ART initiation was 29.1 days (IQR: 14.1 – 62.1) (paper) compared to 27 days (IQR: 12.9 – 50.1) (EMR).

Conclusion:
EMRs can improve quality of HIV care through appropriate placement of ART-eligible patients on treatment in resource limited settings. However, other non-EMR factors influence timely initiation of ART.
4.1  Introduction

Electronic Medical Record (EMR) systems have been shown to significantly improve the quality of healthcare through improved availability of high quality data for clinical decision making (1,2) Additionally, EMRs improve adherence to treatment guidelines resulting in better management of chronic illnesses (3,4) which often require collection of complex data that is longitudinal (5). The easy retrieval of electronic data and automated reports through EMRs can provide information on compliance or non-compliance with key conditions in the clinical guidelines and timeliness of laboratory tests to monitor disease progression and response to treatment (4).

Studies conducted in sub-Saharan Africa (SSA) have shown improvement in time-dependent events following the introduction of EMRs, such as time to process and analyze laboratory specimens, patient waiting time and duration of hospitalization (5-7). Expansion of health systems in many African countries has been hampered by weak infrastructure, lack of adequate skilled health workers, lack of or poor policies and inadequate funding. EMRs provide a unique opportunity to enhance clinical care by integrating systems that have been demonstrated to work in developed countries (8,9). As HIV remains a major public health problem in SSA, which is home to two-thirds of the world’s 34 million HIV-infected persons, substantial global funding for the management of this disease has led to increased investment in EMRs in order to manage the complex data for monitoring the life-long treatment of those infected (10,11).

The wide-scale availability of antiretroviral therapy (ART) has significantly reduced HIV-related morbidity and mortality since 2000 (12-14). As of December 2011, 54% of 14.8 million patients eligible for ART globally were receiving ART. The majority (75%, n=6 million) of those receiving ART were in SSA (14). As of September 2012, approximately 600,000 patients were receiving ART out of 1.5 million HIV-infected persons in Kenya (15). WHO guidelines define conditions for ART eligibility based on the clinical presentation of the patient (WHo staging) and on the immunological status assessed using CD4+ T-cell count (16-18). Despite the global decline in mortality among HIV-infected patients, the number of deaths still remains high in SSA as many eligible patients are not initiated on ART or are initiated late, when the disease is in advanced stages. This is evident through advanced clinical signs or low baseline CD4+ T-cell count indicative of a weakened immune system (19). Although CD4+ T-cell count testing is a routine laboratory measurement for patients enrolled in HIV care programs, test results are not always available for clinical management of patients due to breakdown of flow cytometry equipment, lack of reagents or poor recording and can contribute to late or inappropriate initiation of ART (20,21). Clinicians may also fail to recognize immunological treatment failure which may delay necessary changes in ART regimen.

There is no published evidence that EMRs can improve adherence to clinical guidelines on placement of ART-eligible patients on treatment in resource-limited settings. The purpose of this study was to assess the effect of transitioning from the use of paper-based to an EMR-based system for HIV patient data management on timely initiation of ART among eligible patients and timely performance of CD4+ T-cell count test as described in the Kenya national HIV treatment guidelines (22).

4.2  Methods

This study was conducted at 17 out of 122 rural health facilities in Siaya County in Western Kenya providing HIV care and treatment services. The 17 government-owned clinics are among
20 facilities where the Kenya Medical Research Institute (KEMRI) provides data management and Information and Communications Technology (ICT) support. Three clinics that were excluded from this study did not have electric power or a secure location for a computer at the time of the study. All these facilities have transitioned from the use of paper-based to EMR-based system for management of patient data. EMRs were installed at the facilities on varying dates ranging from September 2009 to June 2012. The clinics included 4 district hospitals (level 4, headed by a physician and provide full inpatient and outpatient care, offering access to select specialized services), 11 health centers (level 3, headed by a clinical officer and provides the lowest level of in-patient care, in addition to out-patient and maternity services); and, 2 dispensaries (level 2, headed by a nurse and provide the lowest level of facility-based out-patient service delivery) (23).

4.2.1 ART eligibility and appropriate placement of patients on ART

The Kenyan Ministry of Health (K-MOH) guidelines for ART (22) were adapted from the WHO guidelines which were published in 2007 and revised in 2010 (24). The K-MOH guidelines recommend using the patient’s clinical status (WHO staging) and CD4 cell count as key determinants when assessing eligibility for placement of patients on ART. In this paper, appropriate placement refers to the guideline-based initiation of ART among eligible patients.

4.2.2 WHO Clinical Staging

The WHO clinical staging uses clinical parameters to categorize HIV infection into 4 stages that reflect on disease severity and prognosis (18,24). WHO clinical stages I and II are often associated with early HIV infection and manifest as conditions such as minor skin diseases and upper respiratory tract infections. WHO clinical stages III and IV are associated with advanced HIV disease and may manifest as one or more diseases such as extra pulmonary tuberculosis, esophageal candidiasis and Kaposi sarcoma and are used to confirm eligibility for initiation of ART. WHO staging is used mainly to help clinicians to make decisions on ART eligibility in health facilities which have no immediate access to CD4+ T-cell count testing.

4.2.3 CD4+ T-cell count and ART eligibility

CD4+ T-cell counts serve as the most important laboratory-based measurement of the state of immunosuppression among patients with HIV and is a main prognostic indicator of patients starting ART (22). The current K-MOH guidelines, which were implemented in 2011, recommend ART initiation among patients aged 2 years or older with the following conditions: (i) CD4 ≤ 350 cells/µl, and stage I or II disease; and (ii) WHO stage III and IV irrespective of CD4 cell count. The K-MOH guidelines recommend initiation of ART for all HIV-infected children under the age of 2 years, irrespective of immunological status measured using CD4+ T-cell counts.

4.2.4 Study population

The study population consisted of male and female patients aged 2 years or older, enrolled in HIV care not more than one year prior to the implementation of an EMR at the clinic. For example, we excluded patients enrolled in HIV care before June 2008 at clinics where an EMR was installed in June 2009. We also excluded ART-eligible patients who were initiated on ART within two months of EMR installation as we considered this to be the learning and transition
Finally, we excluded patients who had already initiated ART treatment elsewhere prior to transferring into the participating health facility due to unavailability of data on baseline CD4 measurements prior to ART initiation and date of ART eligibility.

4.2.5 Paper-based system

In the paper-based system, patient data were captured using a K-MOH approved Comprehensive Care Clinic Card (MOH 257) which collected data on: demographic and contact details of the patient, treatment support information, HIV testing and treatment history, allergies, HIV treatment eligibility and ART regimen (first or second line ART), vital signs, co-infections (including tuberculosis screening and treatment status and other opportunistic infections), laboratory test results for treatment monitoring (including CD4+ T-cell counts, hemoglobin, and amino alanine transferase (ALT)), treatment outcomes (including death, transfer-out, loss to follow-up and interrupted treatment), and appointment date for the next visit. Additional notes were recorded on plain paper and filed together with the MOH 257 in the patient charts.

Treatment data from MOH 257 were manually transcribed into the national ART register, and used mainly to provide summary statistics for routine reporting to K-MOH. The date of next visit recorded on the MOH 257 was used for scheduling patient visits for each clinic day. The clinicians read through the patient notes during each clinic visit to review trends in vital signs, patient promptness with appointments, CD4+ T-cell counts, and other laboratory-based treatment monitoring parameters.

4.2.6 Transition to Electronic Medical Record (EMR) system

The EMR system also referred to as Comprehensive Care Centre Patient Application Database (C-PAD) was developed in 2007. The C-PAD EMR version used for this study was a standalone application developed using Visual Basic for Applications (VBA) and an MS-Access database. Clinicians record data on the paper-based MOH 257 form during each patient encounter. Each clinic has a data entry clerk who enters these data into C-PAD immediately after the visit. These data are used to generate summary reports that are available for the clinician’s review during the weekly clinical review meetings that are also attended by nurses and data clerks. The system has been programmed to ensure that mandatory variables such as demographic data, vital signs, medication and key laboratory measurements are entered. If these essential variables, including demographic data, vital signs, medication, and laboratory measurements were missing from the MOH 257 form, the data clerks contacted the clinician to ensure that missing data were provided and entered into the EMR, as functionally required by the EMR system. To update the system’s database, historical treatment data from the paper-based system were entered retrospectively for all patients who had been initiated on treatment prior to the EMR system installation.

For comparison purposes, retrospective data from the paper systems were entered into the C-PAD system at the participating health facilities.
4.2.7 Outcome measures

The following outcomes were analyzed to measure the quality of HIV care received: (1) The proportion of patients eligible for ART based on CD4+ count or WHO clinical staging who initiate therapy; (2) the time from eligibility for ART to actual ART; and (3) the time from ART initiation to the first CD4+ T-cell count test following ART.

We compared these outcomes before (paper-based system) and after (C-PAD EMR) the EMR system was introduced in the facilities. For each site, the date of C-PAD installation was used to compare the outcome measures during the paper-based versus the EMR based data management.

4.2.8 Statistical Analysis

We included records of patients that were eligible for ART based on the Kenyan ART treatment guidelines (22). We excluded patients that did not have an ART eligibility date but had an ART initiation date and records with an earlier date of ART initiation compared to the ART eligibility date. We included records of patients who were enrolled in HIV care using paper-based system and who subsequently became eligible for ART after the installation of EMRs since the duration of follow-up for majority of these patients was much longer on paper system than follow-up on EMR before they became eligible for ART.

In univariate analysis, frequencies and proportions were reported for categorical variables and median and inter-quartile range (IQR) were reported for continuous variables. The survivor function measurement was used to calculate median time to event. Patients who had not encountered the anticipated time-based events were censored on the date of the last visit. Kaplan-Meier survival graphs were used to compare time-to-event analysis (time from eligibility to ART initiation and time from ART initiation to first CD4+ cell count) between the paper-based and EMR system. The log rank test of equality was used to test for differences in the rate of occurrence of the time-based events between the paper-based system and the EMR system. Pearson’s chi-squared test was used to test for the statistical difference between proportions of eligible patients that were not receiving ART (under-treated) and those that were receiving ART, before and after implementation of the EMR system.

Potential associations between EMR use and ART initiation were also assessed in bivariate analysis using logistic regression expressed as Odds Ratio (OR) and corresponding 95% confidence intervals (CI). All variables in Table 4.2 were entered into a multiple logistic regression model, irrespective of their statistical significance level, to identify predictors that were independently and significantly associated with EMR use and ART initiation. Cox proportional hazards regression models, expressed in Hazard Ratios (HR) and corresponding 95% CI, were used to identify factors associated with time to ART initiation and time to CD4+ cell count test. All variables in Table 4.2 were entered into a Cox proportional hazards regression model, irrespective of their statistical significance level, to test for factors independently associated with the time from eligibility for ART to initiation of ART and time to first CD4+ T-cell test using adjusted hazard ratios (aHR) and corresponding 95% CI. We allowed for potential site-level clustering using generalized estimating equations in the logistic and Cox regression models. Stata version 12.1 (StataCorp, Texas, USA) was used to perform the statistical analysis.
4.2.9 Ethical Considerations

The study was approved by the Associate Director for Science at the Division of Global HIV/AIDS of the US Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI) institutional review board. Individual patient data were de-identified by the KEMRI staff responsible for primary data collection prior to analysis.

4.3 Results

Of the 11,637 patients aged 2 years or older enrolled in HIV care programs not more than one year prior to the implementation of the EMR, a total of 7,308 patients were eligible for ART based on their CD4+ T-cell count or WHO staging. We further excluded records from 1 patient who had no ART eligibility date but had an ART initiation date. In addition, we excluded 9 records that had an earlier ART initiation date than the date of ART eligibility. Among the remaining 7,298 eligible patients, 54.8% (n=3,998) were enrolled in HIV care using a paper-based system while 45.2% (n=3,300) were enrolled after the implementation of an EMR (Table 4.1). In total, 5,990 (82.1% of eligible patients) were receiving ART, including 3,595 (60.0%) female and 2,395 (40.0%) males. The median age of patients enrolled using paper-based systems was 31.6 years (IQR: 25.3 – 40.3) compared to 31.6 years (IQR: 24.8 – 40.5) for patients enrolled after transitioning to EMR. Median baseline CD4+ T-cell count after enrollment in HIV care was 324 cells/µl (IQR: 202 – 486).

4.3.1 ART initiation among eligible patients

Use of EMR was significantly associated with an improved ART initiation among patients compared to the paper-based system [OR = 1.44 (95% CI: 1.23 – 1.68)] (Table 4.2). After adjusting for patient’s sex, age, WHO stage and level of health facility, EMR was independently associated with a 22% increase in the odds of initiating ART among eligible patients [aOR = 1.22 (95% CI: 1.12 – 1.33)] compared to paper-based systems. After excluding the six clinics that had no patients eligible for ART during the data collection period (facility IDs 12, 13, 14, 15, 16 and 17) the odds of ART initiation among eligible patients was [OR = 1.49 (95% CI: 1.28 – 1.71)] and [aOR = 1.21 (95% CI: 1.10 – 1.32)].

During the period in which the facility used the paper-based system, 20.3% (n=811) of patients were eligible for ART but were not receiving ART versus 15.1% (n=497) of patients who were eligible for ART after implementation of EMR system ($\chi^2$ = 33.5; $p$<0.01).

4.3.2 Time from ART eligibility to actual initiation of ART

The median time from ART eligibility to initiation was 29.1 days (IQR: 14.1 – 62.1) in the paper-based system compared to 27 days (IQR: 12.9 – 50.1) in the EMR system. The median time to ART initiation remained unchanged after excluding the clinics with no patients eligible for ART. However, the IQR got narrower in the paper group. Median time (excluding facility ID 12, 13, 14, 15, 16 and 17) was 29.1 days (IQR: 30.0 – 63.9) – paper, and 27.0 days (IQR: 12.9 – 50.1) – EMR. Of the patients eligible for ART, 84.5% [95% CI: 82.4 – 86.4] had initiated ART 3 months from date of eligibility using paper-based system compared to 90.2% [95% CI: 88.4 – 91.7] using EMR system (Figure 4.1). EMR use was associated with a 25% increase in Hazard Ratio of initiation of
ART among eligible patients \[\text{HR} = 1.25; 95\% \text{ CI } 1.02 – 1.52\]. After adjusting for patient’s sex, age, WHO stage and level of health facility, the adjusted Hazard Ratio of ART initiation after implementation of an EMR was 1.36 \(95\% \text{ CI: } 1.20 – 1.53\).

### Table 4.1: Number of patients, by health facility, enrolled on HIV care, eligible for ART and those initiated on ART using paper and EMR systems

<table>
<thead>
<tr>
<th>Facility ID</th>
<th>Facility level*</th>
<th>EMR installation date</th>
<th>Enrolled in HIV care</th>
<th>Eligible for ART</th>
<th>Initiated on ART: n (%)**</th>
<th>Enrolled in HIV care</th>
<th>Eligible for ART</th>
<th>Initiated on ART: n (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>11/1/2011</td>
<td>114</td>
<td>62</td>
<td>58 (93.5)</td>
<td>55</td>
<td>30</td>
<td>29 (96.7)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>8/1/2010</td>
<td>1,343</td>
<td>875</td>
<td>717 (81.9)</td>
<td>1,153</td>
<td>700</td>
<td>627 (89.6)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>10/1/2011</td>
<td>208</td>
<td>127</td>
<td>101 (79.5)</td>
<td>37</td>
<td>11</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>12/1/2009</td>
<td>601</td>
<td>356</td>
<td>296 (83.1)</td>
<td>886</td>
<td>455</td>
<td>400 (87.9)</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>11/1/2011</td>
<td>101</td>
<td>55</td>
<td>53 (96.4)</td>
<td>46</td>
<td>22</td>
<td>20 (90.9)</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>12/1/2010</td>
<td>232</td>
<td>161</td>
<td>144 (89.4)</td>
<td>284</td>
<td>189</td>
<td>159 (84.1)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>10/1/2011</td>
<td>253</td>
<td>126</td>
<td>118 (93.7)</td>
<td>49</td>
<td>18</td>
<td>15 (83.3)</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>8/1/2010</td>
<td>595</td>
<td>349</td>
<td>297 (85.1)</td>
<td>308</td>
<td>176</td>
<td>158 (89.8)</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>9/1/2009</td>
<td>1,478</td>
<td>1,082</td>
<td>802 (74.1)</td>
<td>1,743</td>
<td>1,164</td>
<td>961 (82.6)</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>11/1/2011</td>
<td>204</td>
<td>100</td>
<td>84 (84.0)</td>
<td>20</td>
<td>3</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>12/1/2009</td>
<td>658</td>
<td>506</td>
<td>340 (67.2)</td>
<td>844</td>
<td>532</td>
<td>421 (79.1)</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>6/1/2012</td>
<td>1</td>
<td>1</td>
<td>0 (0.0)</td>
<td>0</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>6/1/2012</td>
<td>96</td>
<td>60</td>
<td>54 (90.0)</td>
<td>0</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>6/1/2012</td>
<td>159</td>
<td>61</td>
<td>55 (90.2)</td>
<td>6</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>7/1/2012</td>
<td>30</td>
<td>20</td>
<td>14 (70.0)</td>
<td>1</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td>6/1/2012</td>
<td>73</td>
<td>33</td>
<td>30 (90.9)</td>
<td>0</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>7/1/2012</td>
<td>59</td>
<td>24</td>
<td>24 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>6,205</td>
<td>3,998</td>
<td>3,187 (79.7)</td>
<td>5,432</td>
<td>3,300</td>
<td>2,803 (84.9)</td>
</tr>
</tbody>
</table>

* Facility level: 2 = Dispensary, 3 = Health Center, 4 = District Hospital. Detailed description of facility types is provided in the Methods section (page 4).

** The percentages in parenthesis are calculated using number patients initiated on ART as the numerator, and the number of patients eligible for ART as the denominator.

### 4.3.3 Time from ART initiation to first CD4 test following initiation

Among the 5,990 patients receiving ART, 3,458 (57.7\%) had at least one CD4+ T-cell count test after initiation of ART. The median time from ART initiation to first CD4+ T-cell count test was 6.27 months (IQR: 4.27 – 10.70) and 6.17 months (IQR: 4.63 – 11.43) for paper and EMR based systems, respectively. Six months after ART initiation, 46.1\% \(95\% \text{ CI: } 44.0 – 48.2\) of the patients receiving ART and enrolled using the paper-based system had had at least CD4+ T-cell count test compared to 45.5\% \(95\% \text{ CI: } 43.1 – 47.9\) of patients using the EMR system (Figure 59).
EMR use was not significantly associated with the hazard of conducting first CD4 test after initiation of ART (HR = 0.94, 95% CI: 0.68 – 1.28). After adjusting for sex, age, WHO stage and facility level, the aHR = 0.98 [95% CI: 0.74 – 1.28].

Table 4.2: Association between EMR and ART initiation among eligible patients, Location, Year

<table>
<thead>
<tr>
<th>Variable</th>
<th>ART initiation</th>
<th></th>
<th>Adjusted Odds Ratio [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio [95% CI]</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paper based system</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR system</td>
<td>1.44 [1.23 – 1.68]</td>
<td>&lt;0.01</td>
<td>1.22 [1.16 – 1.33]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.22 [1.10 – 1.36]</td>
<td>&lt;0.01</td>
<td>1.04 [0.91 – 1.18]</td>
<td>0.35</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.00 [1.00 – 1.00]</td>
<td>0.53</td>
<td>1.01 [1.00 – 1.01]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHO Stage 1</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Stage 2</td>
<td>0.93 [0.30 – 2.84]</td>
<td>0.89</td>
<td>0.91 [0.25 – 3.35]</td>
<td>0.89</td>
</tr>
<tr>
<td>WHO Stage 3</td>
<td>0.01 [0.00 – 0.05]</td>
<td>&lt;0.01</td>
<td>0.16 [0.00 – 0.05]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WHO Stage 4</td>
<td>0.01 [0.00 – 0.03]</td>
<td>&lt;0.01</td>
<td>0.01 [0.00 – 0.04]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Level 2 facility</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3 facility</td>
<td>1.12 [0.53 – 2.38]</td>
<td>0.76</td>
<td>1.07 [0.90 – 1.28]</td>
<td>0.46</td>
</tr>
<tr>
<td>Level 4 facility</td>
<td>0.64 [0.29 – 1.41]</td>
<td>0.27</td>
<td>0.79 [0.68 – 0.92]</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Figure 4.1: Time from eligibility to ART initiation among patients receiving ART in Siaya County, western Kenya.
Figure 4.2: Time from ART initiation to first CD4+ T-cell count test among patients receiving ART in Siaya county, western Kenya

4.4 Discussion

EMR use was associated with a 22% increase in the odds of ART initiation among eligible patients enrolled into HIV care after transitioning from a paper-based system. Although the study showed a 7% reduction in the time from ART eligibility to ART initiation following the introduction of an EMR (from 29.1 days down to 27 days), this was not clinically significant. The study also showed that about eighty percent of patients eligible for ART had been initiated on therapy. Although this proportion is higher than the 56% coverage that UNAIDS reported for SSA at the end of 2011 (14), some 20% of eligible patients are still not receiving ART which may mean under-treatment of these patients. Although EMR use was not significantly associated with a reduction in time to conduct CD4+ T-cell test following ART initiation, the duration using both paper and EMR systems was comparable to the six months recommended in the K-MOH treatment guidelines (22).

EMR use increased the chances of patients turning up at the clinic for ART initiation but not how fast they came. The difference in time from ART eligibility to ART initiation between the EMR and paper groups was marginal suggesting that EMR use did not influence timely initiation of ART despite the weekly generated list of eligible patients that were not receiving treatment. Non-EMR factors such as clinician behavior (provider practice) (25;26) and the time for preparation of patients for ART which includes adherence counselling prior to ART initiation to improve compliance to the treatment regimen (22) and the patient’s own readiness to initiate ART could have contributed to the relatively unchanged time to treatment initiation. On the
other hand, without a reminder (whether lists generated by an EMR or other systems), the need to thoroughly review patient notes to verify eligibility can be overwhelming to clinicians who may in some cases forget to initiate ART among eligible patients resulting in a missed opportunity for appropriate ART initiation. This scenario is more likely in busy clinics or when the patient’s clinical presentation does not indicate they are eligible for ART. The missed opportunity of not providing appropriate treatment to 22% of the 4,000 patients using paper-based system translates to 880 patients not being appropriately placed on treatment. It has been shown that late initiation of treatment results in poor outcomes which include increased mortality (27). Level 4 facilities seemed to be negatively associated with initiation of ART among eligible patients. This could be due to the high volume of patients receiving HIV care at these facilities served by a small number of over-worked clinicians.

A key strength of our study is that it was conducted in multiple sites using the same K-MOH ART guidelines, hence a large sample size which improved the precision of the estimates. All 17 participating health facilities had similar administrative, managerial and laboratory procedures as well as drug regimens.

Our study was not without limitations. Since the retrospective study was based on routinely collected data from rural health facilities, we had challenges with the data quality; for example, we excluded records that did not have an ART eligibility date but had an ART initiation date, or those with an earlier date of ART initiation than the ART eligibility date. Additionally, we excluded from analysis records which had an eligibility date later than the date of ART initiation. However, such records were less than 1% of all the records included in the analysis and therefore had minimal impact on the results. It was difficult to determine whether patients that had no recorded ART eligibility date but were on therapy (n=10) were actually over-treated. EMRs had only been in use for approximately 6 months in a few facilities, which potentially impacted on data quality. Appropriate initiation of ART as recommended in the clinical guidelines is influenced by several factors such as clinician’s practice, patient’s behavior and preference, and societal factors. These factors potentially confounded the true association of EMRs and ART initiation. The challenges reported in transitioning from paper to EMR systems were not unique to our study; limited technical skills, poor data quality and poor infrastructure (including frequent power outages) were also reported by Fraser and Williams (8;9). Other temporal factors such as improved knowledge of health workers, better access to CD4+ T-cell count testing equipment could have also contributed to the observed improvements over time. The benefits of EMR use in improving quality of care can potentially be used to inform policies around the use of technology based solutions in clinical settings in SSA. In an environment of stiff competition for resources, there is need for tangible evidence to convince decision makers to invest resources in technologies that have been shown to improve efficiency and adherence to treatment guidelines.

4.5 Conclusion

In conclusion, we found that EMRs can improve quality of HIV care through appropriate placement of ART-eligible patient on treatment in resource-limited settings. However, other non-EMR factors influence timely initiation of ART. There is room for improvement in adherence to clinical guidelines. Rigorous evaluation studies are needed to demonstrate associations between decision support systems implemented in EMRs and important quality of HIV care indicators such as retention on treatment.
Acknowledgements:
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Reference List

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Chapter 5

The effect of electronic medical record-based clinical decision support on HIV care in resource-constrained settings: A systematic review


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Xenophon Santas  
Daniel Kwaro  
Martin Were  
Paul Biondich  
Christopher Bailey  
Ameen Abu-Hanna  
Nicolette de Keizer
Co-authors’ contribution

T. Oluoch, A. Abu-Hanna and N. de Keizer conceptualized the systematic review and formulated the search criteria. T. Oluoch and N. de Keizer conducted the literature review, scoring and classifying the articles included in the review. T. Oluoch, X. Santas, D. Kwaro and N. de Keizer drafted the manuscript. M. Were, P. Biondich and C. Bailey edited the manuscript and provided input on studies resource-limited context. All co-authors edited and reviewed the final manuscript and consented to its publication.
Abstract

Background
It is estimated that one million people infected with HIV initiate anti-retroviral therapy (ART) in resource-constrained countries annually. This occurs against a background of overburdened health workers with limited skills to handle rapidly changing treatment standards and guidelines hence compromising quality of care. Electronic medical record (EMRs)-based clinical decision support systems (CDSS) are considered a solution to improve quality of care. Little evidence, however, exists on the effectiveness of EMR-based CDSS on quality of HIV care and treatment in resource-constrained settings.

Objective
The aim of this systematic review was to identify original studies on EMR-based CDSS describing process and outcome measures as well as reported barriers to their implementation in resource-constrained settings. We characterized the studies by guideline adherence, data and process, and barriers to CDSS implementation.

Methods
Two reviewers independently assessed original articles from a search of the MEDLINE, EMBASE, CINAHL and Global Health Library databases until January 2012. The included articles that evaluated or described the implementation of EMR-based CDSS that were used in HIV care in low-income countries.

Results
A total of 12 studies met the inclusion criteria, 10 of which were conducted in sub-Saharan Africa and 2 in the Caribbean. None of the papers described a strong (randomized controlled) evaluation design.

Guideline adherence: One study showed that ordering rates for CD4 tests were significantly higher when reminders were used.

Data and process: Studies reported on reduction in data errors, reduction in missed appointments, reduction in missed CD4 results and reduction in patient waiting time. Two studies showed a significant increase in time spent by clinicians on direct patient care. Barriers to CDSS implementation: Technical infrastructure problems such as unreliable electric power and erratic Internet connectivity, clinicians’ limited computer skills and failure by providers to comply with the reminders are key impediments to the implementation and effective use of CDSS.

Conclusion
The limited number of evaluation studies, the basic and heterogeneous study designs, and varied outcome measures make it difficult to meaningfully conclude on the effectiveness of CDSS on quality of HIV care and treatment in resource-limited settings. High quality evaluation studies are needed. Factors specific to implementation of EMR-based CDSS in resource-limited setting should be addressed before such countries can demonstrate its full benefits. More work needs to be done to overcome the barriers to EMR and CDSS implementation in developing countries such as technical infrastructure and care providers’ computer illiteracy. However, simultaneously evaluating and describing CDSS implementation strategies that work can further guide wise investments in their wider rollout.
5.1 Introduction

The 2010 Progress Report “Towards Universal Access” for HIV services reported that 5.25 million people infected with HIV in low-middle income countries were receiving life-saving antiretroviral therapy (ART) at the end of 2009, representing an increase of 1.2 million people since December 2008 [1]. The greatest proportion of these patients (74%) were in sub-Saharan Africa. HIV/AIDS is a chronic disease and treatment guidelines require that patients on ART visit health care providers monthly, resulting in ongoing collection of longitudinal data to monitor treatment [2, 3, 4]. Case finding, enrolling in pre-ART care, tracking CD4 levels regularly, starting ART treatment, ensuring adherence and monitoring side effects are essential components of HIV care. The rapid annual increase in number of patients in a setting of overworked clinical staff with limited training potentially compromises quality of care and requires solutions that enable optimal care provision. Electronic medical record (EMR) systems are considered to be such a solution, especially when they support the implementation of guidelines through Clinical Decision Support Systems (CDSS) [5, 6].

The use of EMR-based CDSS has been shown to improve quality of health care. This has been demonstrated through better diagnosis, reduced medication errors [5, 7] and improved practitioner performance [8]. Studies conducted in the US and other developed countries have shown that CDSS can improve quality of HIV care through improved compliance with guidelines [9, 10]. On the other hand, a systematic review by Tawadrous et al. showed that many studies were often limited by the evaluation method used and benefits can only be reported selectively [11].

The increasing number of patients enrolling on HIV treatment has led to an increase in the number of EMRs developed to document, monitor and manage patient care in developing countries [6]. As with other health care innovations, EMRs and CDSS must be rigorously evaluated to establish their benefits before scaling up their use in clinical practice. Many systematic reviews on CDSS that have been conducted and published such as [8, 11, 12], describe experiences from developed countries. None has so far focused on resource-constrained settings where unique challenges and barriers to implementation of EMRs are encountered. To justify further investment of resources from a highly competitive funding environment for the development and implementation of EMRs with CDSS in resource-poor countries, evidence on their benefits, barriers and overall impact on health outcomes is needed.

We conducted a systematic literature review to identify published original studies on EMR-based CDSS describing process and outcome measures as well as reported barriers to their implementation in resource-constrained settings. We characterized the studies by adherence to clinical guidelines, data and process, and implementation barriers.

5.2 Methods

In this review, CDSS is defined as a computerized information system that matches individual patient characteristics to a computerized knowledge base or software algorithms to generate patient-specific and aggregate recommendations. The recommendations are delivered to the clinician via, for example, computer screen monitors, mobile phones, or printouts in patient notes as alerts or reminders.
We searched for original articles in English using MEDLINE, EMBASE, CINAHL and The Global Health Library (GHL) databases. All studies published prior to the search date (January 2012) were included. Figure 5.1 shows the two search strategies used and the corresponding profile for the searches. In strategy 1, keywords and Medical Subject Heading (MeSH) terms indicative of Electronic Medical Records (A) were combined with terms related to Decision Support Systems (B) and infectious or chronic diseases (F), including HIV and TB (D and E respectively). In strategy 2, keywords and MeSH terms currently used to refer to EMRs (A), Decision Support Systems (B) mobile systems (C) and infectious or chronic diseases (F) including HIV (D) and TB (E). The results of these two strategies were combined using the boolean operator “OR”.

The inclusion criteria were:

(i) The study must describe or evaluate an implementation of an EMR-based CDSS
(ii) EMRs must be used to provide care to persons with an infectious or chronic disease (including HIV or TB)
(iii) The study should have been conducted in a resource-constrained setting

Two reviewers (TO and NdK) independently examined the titles and abstracts to ensure they met the inclusion criteria. In case of discrepancies, a decision whether to include the paper or not was arrived at through consensus. Articles that did not have an abstract or the abstract contained insufficient information to inform the decision to include or exclude were retained and the full text articles were downloaded for more detailed review. Papers published in conference proceedings were considered, but only if there was no full journal paper on the same study available. A manual scanning of the references from identified review articles was conducted to complete the search.

5.2.1 Data abstraction

Full text articles from all studies that met the inclusion criteria above were scored. We developed a standardized data abstraction checklist containing 23 attributes/variables (see Table 5.1). The scores from the two reviewers were compared and discrepancies resolved by consensus. Cohen's Kappa coefficient was used to measure the inter-rater agreement on the inclusion or exclusion of the articles. We sent the key variables abstracted to the corresponding authors of the articles included in the review for validation.

5.3 Results

5.3.1 Search

The initial scan based on our search strategies resulted in 2,020 articles, which included 1,981 original papers and 39 systematic reviews. The titles and abstracts for the 2,020 articles were scanned and 1,953 articles were excluded because the primary subject was not EMR/CDSS, the studies were not clearly associated with patient care or guidelines, the studies were conducted in a developed country or the study did not mention use of any clinical information system. Two additional studies were included following manual scanning of bibliographies of included articles. The remaining 69 articles were read for full text review.
Figure 5.1: Keywords and MeSH terms used in the search strategies.

<table>
<thead>
<tr>
<th>Electronic Medical Records:</th>
<th>Decision Support Systems:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Electronic Medical Record</td>
<td>1. Decision Support Systems</td>
</tr>
<tr>
<td>2. Electronic Health Record</td>
<td>2. Clinical Decision Support Systems</td>
</tr>
<tr>
<td>4. Computerized Medical Record</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mobile Services:</th>
<th>HIV:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Handheld</td>
<td>1. AIDS Virus</td>
</tr>
<tr>
<td>2. Cell phone</td>
<td>2. Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>3. Mobile phone</td>
<td>3. Human T Lymphotropic Virus Type III</td>
</tr>
<tr>
<td>4. SMS</td>
<td>4. Human T-Cell Leukemia Virus Type III</td>
</tr>
<tr>
<td>5. Short message service</td>
<td>5. Lymphadenopathy-Associated Virus</td>
</tr>
<tr>
<td>6. 1 or 2 or 3 or 4 or 5</td>
<td>6. Acquired Immune Deficiency Syndrome Virus</td>
</tr>
<tr>
<td></td>
<td>7. Acquired Immunodeficiency Syndrome Virus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tuberculosis</th>
<th>Infectious or chronic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tuberculosis</td>
<td>1. Infectious Diseases</td>
</tr>
<tr>
<td>2. Kochs disease</td>
<td>2. Communicable diseases</td>
</tr>
</tbody>
</table>

**Search Strategy 1:**

\[(A1 \text{ OR } B1) \text{ AND } (D2 \text{ OR } E1 \text{ OR } F5)\]

**Search Strategy 2:**

\[(A1 \text{ OR } C6) \text{ AND } B1 \text{ AND } (D2 \text{ OR } E1 \text{ OR } F5)\]

Bold texts indicate the keywords, MeSH terms or combination of keywords used in the search. For example: using the MeSH term **Decision Support Systems (B1)** in the search engine also searches for other the keywords in the same box (i.e. **Clinical Decision Support Systems and Computerized Decision Support Systems**).
Table 5.1: Variables in the data abstraction tool

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valid values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Sub-Saharan Africa, Latin America, Asia, Europe/N. America</td>
</tr>
<tr>
<td>Point_of_use</td>
<td>Inpatient, outpatient, in/outpatient</td>
</tr>
<tr>
<td>Patient_population</td>
<td>adults, children, adults and children</td>
</tr>
<tr>
<td>Type_of_health_facility</td>
<td>Government, private, faith-based</td>
</tr>
<tr>
<td>Developer?</td>
<td>In-house, third party, vendor</td>
</tr>
<tr>
<td>Implementation</td>
<td>Standalone, networked</td>
</tr>
<tr>
<td>Data_collection</td>
<td>Paper, electronic, paper/electronic</td>
</tr>
<tr>
<td>Data_collection_by</td>
<td>Clinicians, nurses, clinicians/nurses, other clinical staff</td>
</tr>
<tr>
<td>EMR_Deployment</td>
<td>Paper, electronic, paper/electronic</td>
</tr>
<tr>
<td>Duration_of_EMR_use</td>
<td>&lt;6months, 6months – 1 year, 1–2 years, 2–5 years, 5–10 years, &gt;10 years</td>
</tr>
<tr>
<td>EMR_use</td>
<td>Patient management, information management, national reporting, research</td>
</tr>
</tbody>
</table>

Note:

a - More than one category can be selected
b - We defined third party systems as those that were developed by another institution than the one hosting the system
c - We defined active alerts as those that launched proactively as soon as a pre-defined condition was encountered, while passive alerts were described as those that the user had to find.
Figure 5.2: Search strategies and search results

* - Search Strategy 1

** - Search Strategy 2
Based on full paper review, 17 articles were excluded because they did not describe an EMR or CDSS. This included 4 papers describing the use of cell phone reminders to enhance adherence to medication but the cell phone use was not linked to an EMR. Three other articles were excluded because the EMR/CDSS were not described or evaluated in the articles although the articles described studies in which EMRs were used to provide data. An additional 11 studies were excluded as they did not indicate a link between CDSS use and patient care or implementation of clinical guidelines. Finally, we excluded 21 studies conducted in developed countries as well as 4 systematic reviews and commentaries. The inter-rater agreement on the inclusion or exclusion of the 69 articles that we read for full text review was substantial (κ=0.696). Figure 5.2 shows a flowchart of the inclusion process. Table 5.2 shows a list of the 12 articles included in our review.

5.3.2 Study settings

Ten of the twelve studies included in the review were conducted in sub-Saharan Africa (Kenya – 4, Rwanda – 3, Uganda – 2, Botswana – 1) and two in the Caribbean (Haiti). Five of the studies described EMRs implemented in inpatient and outpatient departments while another five articles described systems that were only implemented in outpatient departments. In many of the studies, the EMR supported care and treatment for all HIV patients (pediatric and adult) except in 3 cases which were based on adult HIV clinics and two where the population of the patients served was unclear. All selected studies were conducted between 2003 and 2011.

5.3.3 EMR deployment and use

Nearly all systems (10 out of 12) were developed by a third party entity (see footnote in Table 5.2) and deployed in a computer networked environment. Regenstrief Institute (n=5) and Partners In Health (n=5) were key implementers in the studies included in this review. Both institutions were involved in developing the OpenMRS [13] which succeeded the AMPATH Medical Records Systems (AMRS) [14]. Although the core data model for OpenMRS is the same, the implementation of the system at different study sites varied. Data capture was mainly on paper (8 out of 12). Direct data entry by clinicians at the point of care was described in only one study [15]. The majority of data entry was conducted after patient encounters by data clerks (n=9). Data capture was occasionally done by clinicians (3 out of 12), and in a few cases by nurses. The deployment of EMRS is a combination of paper-capture and computer entry for electronic storage and manipulation.

The systems were used predominantly by clinicians (12 out of 12) for patient management, information management (9 out of 12), for reporting to ministry of health or donors (9 out of 11) and for research (5 out of 11). Other EMR users mentioned in the studies were nurses, researchers, laboratory staff, outreach/social workers, pharmacists, clinic managers and counselors. All, except two studies [16, 17], described an EMR installation at government-owned health facilities. Systems had different levels of maturity when the studies were conducted. The duration of system installation ranged from 6 months to 5 years.

5.3.4 Clinical decision support systems deployment and use

The CDSSs’ feedback was implemented as alerts (5 studies) or reminders (6 studies). One of the studies did not explicitly indicate how CDSS was implemented. In studies conducted by
institutions collaborating with The Regenstrief Institute (n=5), all using OpenMRS, the Arden syntax [18] was used to implement the decision support functionality. In 5 out of 11 cases the alerts and reminders were active, i.e. they were launched proactively as soon as a pre-defined condition was encountered. In the other 5 cases the alerts and reminders were passive, i.e. the user had to request advice. One study [19] did not describe how the CDSS was implemented and could therefore not be classified.

CDSS was mainly implemented to provide alerts and reminders for laboratory orders. In 7 out of 12 studies, reminders and alerts were related to CD4 ordering. Only two studies described the use of CDSS on medication prescription [16, 20]. Fraser et al. describe an alert based CDSS implementation that doctors can use to check the drugs and their doses, allergies and incompatible drug combinations [15], while Sika et al. describe how they have used their system to track medication history, including past and current use of highly active antiretroviral therapy (HAART) [20]. Three studies explicitly described CDSS use for appointments and follow-up of patients who missed scheduled appointments (i.e., defaulting patients) [19, 20, 21]. Decision support systems were implemented at the individual patient level as well as an aggregate level. At the individual level, trends in physical examination, signs and symptoms, and laboratories results were monitored. Although 5 out of 12 articles indicated that aggregate level summaries were produced by the respective systems, they did not describe the indicators generated and how they were used to improve quality of care.

5.3.5  Outcome measures

The majority of the studies (6 out of 12) were descriptive studies and outcome measures were not used or clearly stated. None of the papers described a randomized controlled design to evaluate the impact of CDSS in providing care to HIV patients. In the few cases where they were explicitly mentioned [4, 22, 23, 24, 25], the main outcome measures were error reduction, CD4 ordering rate and time taken by providers to see patients. Table 5.3 summarizes the key outcome measures.

5.3.5.1  Guidelines adherence

Were et al. showed significantly higher ordering rates for CD4 tests in the CDSS intervention clinic compared to the control clinic (53% vs. 38%, OR=1.80, CI 1.34 to 2.42, p<0.0001) [25].

5.3.5.2  Data and process

Although data accuracy is not explicitly included in clinical guidelines, it is an important aspect that contributes to quality of care because providing accurate information about the patient’s diagnosis, medications, and vital signs are essential for monitoring response to treatment and key health outcomes [26, 27]. Amoroso et al. concluded that the implementation of OpenMRS in Rwanda resulted in a 92% reduction in defined data errors and a 32% reduction in the number of CD4 cell counts that did not reach the clinician [22]. Allen et al. also reported a reduction in data errors although the proportion was not stated [23]. A clinical summary generated by an EMR was shown to improve the quality of data stored in the EMRs [4]. Alamo et al. showed a significant reduction in the mean number of missed appointments from 21 pre-EMR to 8 post-EMR (t_{90} = 15.31, p<0.001). They also showed a reduction of missed appointments as a result of loss to follow-up from 10.9% to 4.8% (p= 0.001) [17].
Table 5.2: Final list of articles included in the systematic review (number of patients/facility)

<table>
<thead>
<tr>
<th>#</th>
<th>Author</th>
<th>Location</th>
<th>Patient population</th>
<th>Study design</th>
<th>Type of CDSS</th>
<th>Outcome measures</th>
<th>Results/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Noormohammad et al. [28]</td>
<td>Sub-Saharan Africa, Kenya</td>
<td>96,000</td>
<td>Qualitative</td>
<td>Reminders</td>
<td>Reasons for not using reminders for decision support</td>
<td>Essentials for a successful EMR are: adequate infrastructure, dictionary maintenance, data quality and staff training.</td>
</tr>
<tr>
<td>2.</td>
<td>Tierney et al. [21]</td>
<td>Sub-Saharan Africa, Kenya</td>
<td>45,000</td>
<td>Descriptive</td>
<td>Reminders</td>
<td>None</td>
<td>The main incentive for clinicians to complete encounter forms is if it meets their information needs. EMRs contribute positively to HIV patient care. Inadequate skilled staff hinders implementation of EMRs.</td>
</tr>
<tr>
<td>3.</td>
<td>Siika et al. [20]</td>
<td>Sub-Saharan Africa, Kenya</td>
<td>4,000</td>
<td>Descriptive</td>
<td>Reminders</td>
<td>None</td>
<td>Standardized patient data collection, faster data retrieval, evidence based decision making and patient care are essential to success EMR implementation.</td>
</tr>
<tr>
<td>5.</td>
<td>Amoroso et al. [22]</td>
<td>Sub-Saharan Africa, Rwanda</td>
<td>10,000</td>
<td>Pre-post</td>
<td>Alerts</td>
<td>Error reduction (data quality), trends in CD4 and weights</td>
<td>Multiple strategies are needed for EMR data quality. Automated and user friendly tools assist data quality and improved clinical care.</td>
</tr>
<tr>
<td>7.</td>
<td>Allen et al. [23]</td>
<td>Sub-Saharan Africa, Rwanda</td>
<td>3,400</td>
<td>Descriptive</td>
<td>Alerts</td>
<td>Error reduction (data quality), timely data access</td>
<td>Combining functionality for patient data recording and display, reporting, and quality control in one system reduces the cost and complexity of setting up and maintaining the data management processes.</td>
</tr>
<tr>
<td></td>
<td>Authors</td>
<td>Region</td>
<td>Population</td>
<td>Type</td>
<td>Entity</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------</td>
<td>-------------------------</td>
<td>------------</td>
<td>--------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Were et al. [4]</td>
<td>Sub-Saharan Africa, Uganda</td>
<td>Pre-post</td>
<td>Clinical Summary</td>
<td>Time for patient care and length of patient visit.</td>
<td>EMR-based, patient-specific clinical summaries were associated with improved clinic efficiency and shorter patient visits.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Alamo et al. [17]</td>
<td>Sub-Saharan Africa, Uganda</td>
<td>Pre-post</td>
<td>Alerts</td>
<td>Missed appointments, patients lost to follow-up</td>
<td>CDSS contributed to a significant reduction in number of appointments missed as well as the number of patients lost to treatment follow-up.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Jazayeri et al. [16]</td>
<td>Caribbean, Haiti</td>
<td>Descriptive</td>
<td>Alerts</td>
<td>None</td>
<td>EMRs aid clinical and operational research.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Fraser et al. [15]</td>
<td>Caribbean, Haiti</td>
<td>Descriptive</td>
<td>Reminders</td>
<td>None</td>
<td>Lack of infrastructure, including ICT remains a major challenge to the implementation of EMRs in resource poor settings. However, innovative solutions can be used to track clinical outcomes, laboratory tests and drug supplies.</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.3: Outcome measures of evaluations in included studies.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Article</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guideline adherence:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clinical compliance with CD4 testing guideline.</td>
<td>Were et al [25]</td>
<td>Increased CD4 ordering rate from 42% to 63%.</td>
</tr>
<tr>
<td>• Loss to follow-up</td>
<td>Alamo et al [17]</td>
<td>A reduction in loss to follow-up of patients from 10.9% to 4.8%.</td>
</tr>
<tr>
<td><strong>Data and process:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Data errors</td>
<td>Amoroso et al [22]</td>
<td>92% reduction in defined data errors.</td>
</tr>
<tr>
<td>• Data access</td>
<td>Allen et al [23]</td>
<td>Reduction in data error rate not quantified.</td>
</tr>
<tr>
<td>• Patient visit time</td>
<td>Allen et al [23]</td>
<td>Reduction in data access and communication time not quantified.</td>
</tr>
<tr>
<td>• Missed appointments</td>
<td>Alamo et al [17]</td>
<td>Daily missed appointments reduced from 21 to 8.</td>
</tr>
<tr>
<td>• Patient waiting time</td>
<td>Alamo et al [17]</td>
<td>Patient waiting time to see nurses reduced from 56 min to 38 min.</td>
</tr>
<tr>
<td>• Providers’ free time</td>
<td>Tierney et al [21]</td>
<td>10 minute (23%) reduction in patient visit time.</td>
</tr>
<tr>
<td>• Providers’ time on direct patient care</td>
<td>Were at al [4]</td>
<td>11.5 minute reduction in patient visit time.</td>
</tr>
<tr>
<td>• CD4 result not reaching clinician</td>
<td>Amoroso et al [22]</td>
<td>Increase in provider free time from 15% to 46% of workday.</td>
</tr>
<tr>
<td>• CDA result not reaching clinician</td>
<td></td>
<td>26% increase in time spent on direct patient care (from 2.3 min to 2.9 min).</td>
</tr>
<tr>
<td><strong>Barriers to Implementation:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Reasons for failure of reminder systems</td>
<td>Noormohammad et al [28]</td>
<td>Delayed data entry and pending test results, wrong data inadvertently entered,</td>
</tr>
<tr>
<td>• Challenges to EMR implementation</td>
<td>Fraser et al [12]</td>
<td>inadequate training of providers and resources-related issues.</td>
</tr>
<tr>
<td></td>
<td>Bussmann et al [19]</td>
<td>Lack of infrastructure, including ICT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Few doctors, lack of roads, electricity and electronic communication.</td>
</tr>
</tbody>
</table>
Were et al. reported a statistically significant increase in time spent by providers on direct patient care after the installation of EMR-based clinical summaries (2.9 min vs. 2.3 min, \( p < 0.001 \)) [4]. Returning patients spent 11.5 min less time per visit after implementation of the Patient Summary Reports compared with the pre-intervention period when the OpenMRS encounter forms were used but no summaries were printed (197.7 min before vs. 186.2 min after, \( p < 0.001 \)) [4]. Alamo et al. showed significant reductions in waiting time to see the nurses (38 min post-EMR vs. 56 min pre-EMR; \( Z = -5.13, p < 0.001 \)), and the time to see the pharmacy technician (11 min post-EMR vs. 45 min pre-EMR; \( Z = -7.25, p < 0.001 \)). However, there was an increase in waiting time to see the laboratory technician (42 min post-EMR vs. 15 min pre-EMR; \( Z = 4.35, p < 0.001 \)) [17]. The computerized reminder system identified encounters with overdue CD4 tests (21%) [25].

5.3.5.3 Barriers to CDSS implementation

Infrastructural obstacles were reported as barriers to the implementation of EMRs and hence CDSS. These include unstable electrical power, loss of Internet connectivity, and access to mobile phones. Humidity, dust, and security concerns were also indicated as barriers [15, 16, 19, 21].

Low literacy and poor training of health workers on use of computerized information systems including EMRs remains a major challenge. Skills to extract and analyze data for patient care and research were limited [15, 20]. Tierney et al. noted that inadequate training on medical informatics to EMR developers and health managers remains a major problem [21].

Clinicians often fail to adhere to reminders and alerts for various reasons. Noormohammad et al. reported some factors that are potential barriers to clinician’s using CDSS, specifically, unreliable generation of summaries and reminders, generation of inaccurate reminders, and failure by providers to comply with accurate reminders [28]. Were et al. reported that some clinicians simply disregarded reminders. However, educating them on reminders improved acceptance rates [25].

5.3.6 Quality of study methodology:

Eight of the twelve studies were descriptive and the remaining four had a quasi-experimental study design conducted in single sites. The studies had several limitations such as small sample size, short follow-up period, potential systematic bias, and the majority had no explicit outcome measure.

5.4 Discussion

Our systematic literature review identified twelve studies meeting our inclusion criteria, 10 of which were conducted in sub-Saharan Africa and the other two in the Caribbean. The three studies that reported quantitative evaluation of the effect of CDSS on quality of care showed statistically significant improvement in compliance with ordering critical laboratory investigation (CD4 tests), an increase in time spent directly with patients in health care provision, and a reduction in missed appointments, respectively [4, 17, 25]. The majority of the studies showed that data capture was mainly on paper by clinical staff. Direct data entry into the EMR by
Adherence to clinical practice guidelines is essential for quality provision of health care. Despite efforts and resources invested in developing and disseminating these guidelines, practitioners still ignore them [29]. We found effects of EMR-based CDSS on improved adherence to guidelines related to CD4 ordering and results reaching the clinician, reduction in data errors, and reduction in missed appointments [4, 17, 22] are consistent with work done in the US and other developed countries [9, 30, 31]. Garg et al. showed that CDSS can potentially improve practitioner performance in developed countries [8]. Studies in our review described an increase in the amount of time spent on direct patient care and a reduction in time spent by patients waiting to see the nurse and pharmacists [4, 17]. Alamo et al. indicate an increase in waiting time to see the laboratory technologists. It is not clear from the paper whether laboratory orders were made electronically using a computerized physician order entry (CPOE) hence it is difficult to assess the extent to which the EMRs negatively impacted the waiting time. Published work done elsewhere shows that the use of CPOE generally improves waiting time at the laboratory [32].

Several barriers to CDSS implementation were mentioned in our included articles. Infrastructure problems, clinicians’ limited computer skills, and failure by providers to comply with the reminders are key impediments to implementation and effective use of CDSS. These are quite different from the reasons for not using CDSS in developed countries which include inability to type quickly, reduced eye contact with patients, false alarms and preference to write in long prose [33, 34]. Health facilities in resource-constrained settings encounter unique human resources and infrastructure challenges that are not necessarily experienced in developed countries [35, 36]. This underscores the need for innovative solutions such as power backup and “offline” systems that are appropriate for resource-limited settings [15, 16].

The small number of evaluation studies and the basic evaluation designs show the premature status of implementation and evaluation studies on EMR and CDSS in resource-limited settings despite an annual investment of nearly $1 billion globally on health systems through global health initiatives such the US President’s Emergency Plan for AIDS Relief (PEPFAR) [37] and the Global Fund to fight against AIDS, TB and Malaria (GFATM) [38] since 2003. Implementation of CDSS in developing countries is still uncommon. Two recent systematic reviews by Bryan et al. and Fraser et al. reiterated the need for comprehensive evaluations of CDSS as the use of EMRs in resource-limited settings continues to expand in a standards-based, sustainable manner based on appropriate technologies [39, 40]. More work needs to be done to overcome the barriers to EMR and CDSS implementation in developing countries – including capacity building on health informatics, and simultaneously evaluating and describing CDSS implementation strategies that work in order to inform wise use of limited resources.

Our review was limited by several factors. The studies included in our review were conducted in single sites and the findings may not be easily generalizable. Although we used an extensive search strategy on multiple literature databases we found a small number of evaluation studies meeting our inclusion criteria. Ten of the twelve studies evaluated OpenMRS thereby limiting the generalizability of the findings. The heterogeneity in terms of study designs and outcome measures made it impossible to meaningfully conclude on the effectiveness of CDSS on quality
of HIV care and treatment in resource-limited settings. High quality evaluations grounded on solid scientific principles such as those described in Good Evaluation Practice in Health Informatics (GEP-HI) [41] should be conducted to inform decisions on the most appropriate implementations of systems that work in the developing world. Clear clinical care process and outcomes measures should be defined when conducting such studies.
Reference list


Chapter 6

Effect of a Clinical Decision Support System (CDSS) on Early Action on Immunological Treatment Failure among HIV patients in Resource-Constrained Settings: A Cluster Randomized Controlled Trial in Kenya

Submitted for publication

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Xen Santas
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Samuel Mwalili
Kimeu Muthusi
Nicky Okeyo
Davies Kimanga
Ronald Cornet
Ameen Abu-Hanna
Nicolette de Keizer
Co-authors’ contribution

T. Oluoch, A. Abu-Hanna and N. de Keizer conceptualized and designed the study. A. Katana, D. Kwaro and D. Kimanga reviewed the clinical components of the study and manuscript. S. Mwalili and K. Muthusi were the study statisticians and developed the analysis programs. A. Abu-Hanna double-checked the statistical analysis. P. Langat and N. Okeyo provided oversight to the data management team that conducted the data collection, de-identification and cleaning. X. Santas, J. Ojwang and R. Cornet provided critical review of the manuscript and gave the informatics perspective. All co-authors were involved in the interpretation of the results. T. Oluoch, R. Cornet and N. de Keizer drafted and revised the manuscript. All authors edited and reviewed the manuscript and gave their final approval for submission to the journal.
Abstract

Background
In spite of the ongoing scale-up of antiretroviral therapy (ART) for HIV patients, many countries in resource-limited settings lack accurate information in a form that can support clinical decisions for HIV care.

Methods
We implemented a clinical decision support system (CDSS) that generates alerts on encountering patients experiencing immunological treatment failure and recommends appropriate action based on national treatment guidelines at 13 HIV clinics in western Kenya. We evaluated the effect of this CDSS in a prospective, multi-center, cluster randomized controlled trial on: (1) appropriate action on immunological treatment failure (primary outcome); (2) time from detection of immunological treatment failure to clinical action; and (3) timely ordering of first CD4+ T-cell test after initiation.

Findings
A total of 21,349 patients were receiving ART including 10,358 in control, and 10,991 in intervention sites. CDSS alerts were associated with a higher likelihood of clinicians taking appropriate action on treatment failure (adjusted Odds Ratio – aOR = 2.96 (95% CI: 2.45 – 3.56)). The median number of days from meeting the alert conditions to action was 47 days (Inter-quartile range - IQR: 10 – 116) in the control group compared to 13 days (IQR: 1 – 42) in the intervention group (p<0.001). The Median time from ART initiation to first CD4+ T-cell measurement for control and intervention sites were 12.13 months (5.13 – 12.13) and 6.76 months (2.57 – 11.23) (p <0.0001).

Interpretation
CDSS significantly improved the likelihood of timely and appropriate action on immunological treatment failure among HIV patients. We expect that the strong associations demonstrated can be generalizable to virological monitoring of HIV patients receiving ART once CDSS implement the 2013 WHO HIV treatment guidelines.
6.1 Introduction

The Global Update on HIV Treatment 2013 shows that 9.7 million people with HIV infection living in low-to-middle income countries were receiving antiretroviral therapy (ART) at the end of 2012. Of the 9.7 million people, over 77% (n=7.5 million) live in sub-Saharan Africa (SSA) (1). In 2012, 1.6 million people were newly initiated on ART and the number is likely to increase following the release of the 2013 WHO Guidelines for HIV treatment which recommend broader eligibility criteria for ART and early initiation of treatment (1;2). With the unprecedented scale-up comes a major challenge of early identification and management of those failing first-line ART. First-line ART are the standardized efficacious, cost-effective, widely available and least toxic drug regimens. The consequences of ART failure include increased risk of HIV-associated complications such as opportunistic infections, malignancies and neuro-cognitive dysfunction. Studies conducted in SSA show that 15-25% of people receiving ART experience conditions that define treatment failure (3-6). Although virological failure is the best predictor of ART failure, viral load monitoring for patients on ART remains expensive and often complex to monitor in resource-limited settings, especially in rural areas (6). Many rural clinics in SSA therefore opt for WHO clinical staging and the widely available immunological monitoring based on CD4+ T-cell measurement to monitor response to ART (5;7;8).

The majority of adults and children receiving ART in SSA are enrolled in government-owned HIV clinics, which are often busy and understaffed (9;10). The challenge of managing a chronic disease with complex, longitudinal data in these circumstances negatively affects thorough clinical monitoring (6;11). Clinical Decision Support Systems (CDSS) are computer programs that apply knowledge, often in the form of sets of rules, to data stored in Electronic Health Records (EHR) in order to offer patient-specific and actionable recommendations to improve clinical decisions (12;13). CDSSs communicate recommendations to clinicians through alerts and reminders and have shown potential to improve quality of care, patient safety and patient outcomes in developed countries (14-16). Systematic reviews by Bryan et al. and Oluoch et al. report that very few scientifically rigorous studies have been conducted in SSA to show the effects of CDSS on clinical practice or health outcomes (17;18).

The aim of this study was to determine whether a CDSS that supports detection of, and recommend action on, immunological treatment failure improves appropriate action taking based on treatment guidelines.

6.2 Methods

6.2.1 Study Design

We conducted a prospective, multi-center, clustered randomized controlled trial comparing the effect of an electronic health record (EHR) with CDSS against an “EHR only”, on timely and appropriate action taken by clinicians for HIV patients experiencing immunological treatment failure among those receiving ART in Siaya County, western Kenya.

6.2.2 Study Participants

The study included HIV patients (adults and children) who were eligible for ART based on the Kenyan Ministry of Health (KMOH) HIV treatment guidelines of 2011, which recommended initiating ART among patients classified in WHO clinical stage III or IV (see Appendix 6.1) irrespective of CD4+ T-cell count, or any WHO clinical stage with a CD4+ T-cell count <350 cells/μl (19). Only patients eligible for ART at the participating clinics who had at least two recorded CD4+ T-cell counts on or after 1st Jan 2012 (i.e. 6
months before the implementation of the CDSS) were included in the analysis since at least two CD4+ T-cell measurements are needed to define conditions for treatment failure. HIV-positive pregnant women were not included in the study since the CDSS intervention was not implemented at the Maternal and Child Health (MCH) clinic where pregnant women are followed-up. All CD4+ T-cell testing were performed at laboratories located within the participating health facilities or referral laboratories within Siaya County. The HIV care and treatment guidelines recommend that all HIV patients, irrespective of their WHO clinical stage, have a baseline and follow-up CD4+ T-cell tests performed.

6.2.3 Study sites

All 20 HIV clinics, where the Kenya Medical Research Institute (KEMRI) provides data management support, were invited to participate in the study. The rural clinics were located within the Health and Demographic Surveillance Area where KEMRI conducts a variety of public health studies (20). According to the Kenya HIV estimates report for 2013, the adult HIV prevalence in Siaya County was 23.7% - over four times higher than the national prevalence (21). The health facilities were of three types: (i) Dispensaries, categorized by the Kenya Ministry of Health (KMOH) as level 2 facilities, which provide limited outpatient services focusing on disease prevention and basic curative care and are headed by a nurse; (ii) Health Centers (level 3), which provide outpatient, maternal and child health and limited inpatient services and are headed by a Clinical Officer; and (iii) District Hospitals (level 4), which are principal referral facilities at the district level and are headed by a physician. They offer a complete range of ambulatory, outpatient and inpatient services (22).

The 20 health facilities transitioned from use of paper records to the Comprehensive Care Centre Patient Application Database (C-PAD) EHR for patient data management at varying times from July 2009 to June 2012. The standard EHR (C-PAD) was enhanced to include CDSS functionality and installed at the intervention sites in June 2012. Data collection at each site took 12 months during the period of September 2012 to January 2014.

6.2.4 Exclusion criteria

Health facilities were excluded from the study if they did not have reliable electric power, secure location for a computer, or permanent data clerks to help with the regular data management activities as required by the study protocol (23). Of the 20 HIV clinics invited to participate in the study, 7 met the exclusion criteria and were excluded.

6.2.5 Immunological HIV treatment failure

Immunological treatment failure is defined in the HIV treatment guidelines as any one of the following three conditions: (i) CD4+ T-cell count below the patient’s baseline measurement 6 months after initiation of therapy, (ii) CD4+ T-cell count less than 50% of peak measurement at any time after 6 months of treatment, (iii) CD4+ T-cell count persistently below 100 cells/µl after 12 months of treatment (19).

6.2.6 Intervention: CDSS implemented in EHR

Health facilities participating in the study had one of the two versions of the C-PAD EHR. The version installed at the intervention sites (n=7) had a CDSS implemented with pop-up information about an individual patient whenever action is needed (EHR+CDSS). An alert was generated when a patient
experienced immunological treatment failure. In such cases, the CDSS offered the clinician advice on appropriate action such as adherence counseling for the patient, performing a repeat CD4+ T-cell test, ordering a viral load measurement, substituting drug or switching treatment regimen. The CDSS also generated a reminder on overdue CD4+ T-cell tests, i.e., more than six months after the last CD4+ T-cell test, as defined in the KMOH HIV treatment guidelines (19). More than one action could be recommended. Table 6.1 shows all types of alerts generated by the CDSS and the recommended actions. The condition causing the generation of the alert and the action recommended by the CDSS were printed out and filed on top of the patient notes for immediate clinical action either during the current or the next monthly visit. Where clinicians deemed it necessary to take immediate action, patients were called back to the clinic before their next appointment. Clinicians had the option of overriding the decisions recommended by the CDSS. In that case they were asked to record their reason for not following the system’s recommendation.

The alerts were turned off in the version of C-PAD that supports standard care, which was installed at the control sites (EHR-only). This meant that there were no alerts or recommendations and clinicians relied on weekly summary reports generated at patient level to make decisions on patient management, which is usual care since the implementation of the EHR. The clinical staff and data clerks at the intervention sites were given practical training on the additional functionality and how to read the alerts and act on the recommendations. To avoid contamination, the EHR-only group received refresher training on use of the standard EHR and continued to provide care as usual but received similar routine support visits by the KEMRI data management team as the EHR+CDSS group. Training to both groups made reference to the HIV treatment guidelines whenever necessary.

In order to generate alert data for analyses from the control sites, we retrospectively activated the CDSS alerts at the end of the study.

### 6.2.7 Outcomes measures

The primary outcome measure was the difference in proportion of patients who experienced any of the three conditions that define immunological treatment failure (19) and had a documented clinical action in the control and intervention groups. The secondary outcomes were the effect of CDSS on: (i) time from detection of immunological treatment failure to clinical action (ii) time from ART eligibility to initiation of ART among patients who became eligible during the study period and (iii) time from ART initiation to first CD4+ T-cell measurement. We qualitatively reviewed the most common reason(s) why clinicians ignore the recommendations of the CDSS.

### 6.2.8 Sample size

Sample-size calculations were based on the intention to include 20 facilities: 10 facilities with EHR only or standard EHR (control sites) and 10 facilities with EHR+CDSS (intervention sites). The test of hypothesis was assumed to be two-sided with a significance level of 0.05. A sample of 730 patients per group was required with 80% power to detect a difference between the two groups specifying proportions of patients with clinical action following immunological treatment failure of 35% in the EHR-only group and 75% in the EHR+CDSS group. This sample size was calculated assuming a design effect = 2.0 (for the intra-facility correlation) and that 20% would experience treatment failure (3;6). This resulted in an average of 1460/20 = 73 sampled persons per clinic for each group of 10 facilities. The sample size calculation program was written in SAS statistical software version 9.2, based on Rochon’s article (24).
<table>
<thead>
<tr>
<th>Condition/Reason</th>
<th>Alert generated</th>
<th>Suggested actions by clinician in response to alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 T-cell count is not available.</td>
<td>Please order baseline CD4 test.</td>
<td>1. If result available, write in Blue Card</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. If not available consider the next immediate CD4 as the baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. If none is available Order CD4 test and give reasons why baseline CD4 was not available</td>
</tr>
<tr>
<td>The last CD4 T-cell count was conducted over 6 months before current visit date.</td>
<td>The last CD4 test was conducted over 6 months ago.</td>
<td>1. If result available, write in Blue Card</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Indicated if CD4 test already re-ordered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Re-order CD4 test</td>
</tr>
<tr>
<td>Treatment failure in adults</td>
<td>Check for possible immunological treatment failure.</td>
<td>Same as above</td>
</tr>
<tr>
<td>CD4 count drop to pre-treatment baseline level or below pre-treatment baseline level, twelve months or more after initiation of ART.</td>
<td>Check for possible immunological treatment failure.</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Check on adherence and intervene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Check viral load and intervene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Order viral load test and intervene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Check change of Drugs ( substitution)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Check Nutrition status and intervene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Query if there was a drug stock-out</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Check if patient defaulted and intervene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Check if there is any upcoming social behavior that may interfere with adherence e.g. alcoholism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. Suspect immunologic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. Narrow down the next appointment for close monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11. Do home visits by the staff to identify gaps at home</td>
</tr>
<tr>
<td>CD4 count drop of 50% (or more) from on-treatment peak value during the follow-up period.</td>
<td>Check for possible immunological treatment failure.</td>
<td>Same as above</td>
</tr>
<tr>
<td>Persistent (2 or more) CD4 count less than 100 cell/µl, twelve months or more after initiation of ART.</td>
<td>Check for possible immunological treatment failure.</td>
<td>Same as above</td>
</tr>
<tr>
<td>ART Eligibility for adults</td>
<td>Patient is eligible for ART.</td>
<td>1. Prepare patient for Initiation on ART – adherence counseling, drug counseling/pill burdens</td>
</tr>
<tr>
<td>CD4 &lt;350 cells/ µl (irrespective of pregnancy) and not on ART.</td>
<td></td>
<td>2. Give shorter appointment date</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Check WHO staging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Initiate on care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Check Nutrition status and intervene</td>
</tr>
<tr>
<td>TB/HIV co-infected patient not on ART</td>
<td>Patient is eligible for ART.</td>
<td>1. Change/update WHO staging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Prepare the patient for Initiation within 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Check Nutrition status and intervene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Put on TB care immediately</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Isolate the patient or refer to a TB clinic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Teach the patient on TB infection control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Order CD4 test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Within 2 weeks provide required counseling if client is ready after 2 weeks and/or client is ready then initiate to ARVs</td>
</tr>
<tr>
<td>Treatment failure in children</td>
<td>Check for possible immunological treatment failure.</td>
<td>Same as above</td>
</tr>
<tr>
<td>CD4% of 10 (and below) or absolute count of 200 cells/ µl (or below), 12 months or more after initiation of ART</td>
<td>Check for possible immunological treatment failure.</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Thorough screening for OIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Check/order viral load test and intervene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. With viral load result, If virological failure switch drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Check on child adherence by querying care giver and</td>
</tr>
</tbody>
</table>
### ART eligibility for children

<table>
<thead>
<tr>
<th>Child category</th>
<th>Action 1</th>
<th>Action 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child older than 5 years with CD4 counts of 200 (or below), twelve months or more after initiation of ART</td>
<td>Check for possible immunological treatment failure.</td>
<td>Same as above</td>
</tr>
<tr>
<td>Child less than 18 months regardless of CD4 counts and not on ART</td>
<td>Patient could be eligible for ART. Please conduct confirmatory HIV DNA PCR test.</td>
<td>1. Conduct antibody test, if + conduct PCR, if PCR is + prepare for initiate and initiate when ready 2. Check Nutrition status and intervene</td>
</tr>
<tr>
<td>Child aged between 18-59 months with CD4% less than 25% or CD4 count less than 1000 and not on ART</td>
<td>Patient is eligible for ART but not on ART.</td>
<td>1. Prepare and initiate 2. Check nutrition status and intervene, if needed</td>
</tr>
<tr>
<td>Child aged between 5-12 years with CD4% less than 20% or CD4 count below 500 and not on ART</td>
<td>Patient is eligible for ART but not on ART.</td>
<td>2. Prepare and initiate 3. Check nutrition status and intervene, if needed</td>
</tr>
</tbody>
</table>

#### 6.2.9 Randomization

The unit of randomization was the health facility and not individual patients since all patients enrolled on HIV treatment at any participating clinic received the same level of treatment monitoring based on the type of EHR installed (EHR-only or EHR+CDSS). The KEMRI data management team, used blocked randomization to assign the 13 health facilities into two groups on a ratio of 1:1, matched by MOH level and the number of patients enrolled in HIV care (25). A member of the KEMRI team, who was not part of the study, randomly selected a clinic within each block followed by a selection of a similar clinic matched by the number of patients receiving HIV care within the same block. The 13 clinics were randomized into 6 control sites and 7 intervention sites. Control sites consisted of one dispensary (level 2), three health centers (level 3), and two district hospitals (level 4). Intervention sites consisted of five health centers (level 3) and two district hospitals (level 4). Health facilities participating in the study could not be blinded to allocation due to the character of the intervention. The EMRs installed at control sites were to be upgraded to include the CDSS functionality at the end of the study in case positive associations were found. This is part of the national scale-up of EHRs in Kenya.

#### 6.2.10 Data management

The data elements required for the analysis in this study were extracted directly from the EHR into analysis software. As the data contained missing values for some variables, we performed Little’s test to assess whether data were missing completely at random (MCAR) (26). Based on the significant result obtained ($p<0.0001$), indicating that missingness did not follow MCAR, we fitted a logistic regression model against the observed data to investigate whether one can assume that data were missing at random (MAR). Following confirmation that the data can be assumed as MAR, we used multiple imputation (MI) which provides more efficient inference compared to complete case analysis (CCA) when data is MAR as was the case in our study (27). Markov chain Monte Carlo method was used to impute missing data. We also performed CCA and compared the results with those obtained using MI.
6.2.11 Statistical analysis

We calculated mean and standard deviation, median and inter-quartile range (IQR) to summarize continuous variables, while frequencies, proportions, and 95% confidence intervals (CIs) were calculated to summarize categorical variables. Kruskal-Wallis test was used to compare medians. Logistic regression models were used to assess the effect of CDSS on detecting and acting on immunological treatment failure. Eight (8) patient-level variables (see Table 6.2) and 2 center-level variables (site type/level and duration of EHR use) were used as covariates to adjust for differences in case-mix between intervention and control groups. Generalized Estimating Equations with exchangeable correlation structure were used in the logistic regression models to adjust for potential intra-cluster correlation. Kaplan-Meier plot and Log-rank (Chi-square) test for equality of survivor functions were used to measure statistical differences in the survival curves comparing time-to-event and expressed as a p-value. The data were censored at the last follow-up visit date. The analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and Stata version 13.0 (Stata Corp, College Station, Texas, USA).

6.2.12 Ethical considerations

The study was approved by the Associate Director for Science at the Center for Global Health of the US Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI) institutional review board. Individual patient data were de-identified by the KEMRI staff responsible for primary data collection prior to analysis. CDC and University of Amsterdam staff had no access to the patients or any identifiable patient information.

6.3 Results

A total of 41,062 patients were enrolled in HIV care, including 19,662 and 21,400 patients in control sites and intervention sites, respectively. Among these patients, 52.5% (n= 21,349 including 10,358 in control and 10,991 in intervention sites) were eligible for, and receiving ART (Figure 6.1) and hence included in the analyses. The demographic and clinical characteristics of the patients receiving ART at the control and intervention sites were similar except for WHO clinical stage at enrolment on HIV care where 62.2% were classified in stages I and II in control sites compared to 51.3% in the intervention sites. The median age of the patients was 33 years (IQR: 26 – 43) and median CD4+ T-cell count at enrollment into HIV care was 181 cells/µl (IQR: 89 – 263) and most of the patients (40.7%) were in WHO clinical stage III at the time of enrollment in HIV care. The most common first-line regimens were nevirapine-containing regimens which were prescribed to 86.6% of the patients receiving ART. ART adherence at last visit was 99% (Table 6.2).

6.3.1 Alerts and actions on immunological treatment failure

Of the alerts, 34.3% (2,467/7,192) were indicative of immunological treatment failure. Appropriate action based on the national treatment guidelines was taken on 29.5% (CI: 26.8 – 32.2) in control sites compared to 54.9% (CI: 52.3 – 57.6) of the alerts in the intervention sites (Table 6.3). The unadjusted Odds Ratio (OR) for taking appropriate action at an intervention site was 2.91 (CI: 2.43 - 3.49). After adjusting for the patients’ age, sex, marital status, baseline CD4+ T-cell count, WHO stage and treatment regimen, use of CDSS was independently associated with a higher likelihood of clinicians taking appropriate action.
Figure 6.1: Flow Chart for randomization and study participants from 20 HIV clinics in Siaya County in 2013

Participating clinics supported by KEMRI (n=20)

Exclude clinics with no reliable electric power or secure room for computer (n = 7)

Clinics assigned to the control arm (n=6).

Clinics assigned to the intervention arm (n=7).

All patients enrolled on HIV care (n= 21328)

All patients enrolled on HIV care (n= 19579)

Exclude all pre-ART care patient not eligible for ART (n=10300)

Exclude all pre-ART care patient not eligible for ART (n=9101)

Patients eligible for ART (n=11028)

Patients eligible for ART (n=10478)

Patients eligible for, but not receiving, ART (n=120)

Patients eligible for, but not receiving, ART (n=37)

Patients with recorded alerts for immunological treatment failure (n=332)

96

Patients with recorded alerts for immunological treatment failure (n=1125)

Patients with appropriate action taken on treatment failure alerts (n=737)

Patients with appropriate action taken on treatment failure alerts (n=1342)
on conditions indicative of treatment failure (adjusted Odds Ratio – aOR = 2.96 (CI: 2.45 – 3.56)). The estimates obtained from MI and CC analyses were comparable except for patients with a baseline CD4+ T-cell count of 350 – 500 cells/µl where OR = 2.15 (CI: 1.12-4.12) (CC) compared to OR = 1.65 (CI: 0.94-2.91) (MI) (Table 6.3).

The median number of days from alert to action in the control group was 47 days (IQR: 10 – 116) compared to median of 13 days (IQR: 1 – 42) in the intervention group (Log-rank test for equality p<0.001) (Figure 6.2).

6.3.2 Alerts and actions on ART initiation among eligible patients

The CDSS generated a total of 232 alerts on ART-eligible patients who were not receiving ART. This accounted for 3.2% of all alerts generated. Overall, appropriate action, including pre-ART counseling or enrollment on ART, was taken on 44.4% of the alerts on ART-eligible patients that were not receiving ART. CDSS use was not significantly associated with appropriate initiation of eligible patients on ART (aOR = 1.02 (CI: 0.55 – 1.88)).

6.3.3 Time from ART initiation to first CD4+ T-cell measurement

The median time from ART initiation to first CD4+ T-cell measurement was 6.76 months [IQR: 2.57 – 11.23] in the intervention group and 12.13 months [IQR: 5.13 – 12.13] in the control group. The two curves in Figure 6.3 are significantly different using the Log-rank test of equality (p<0.001).

6.3.4 Reasons for clinicians not acting on alerts

There were instances when clinicians did not act on the recommendation following an alert. In slightly more than 50% of the cases in which the alerts were ignored, clinicians reported that the appropriate action (such as ordering adherence counseling) had been taken but was not recorded before in the patient charts. There were also instances where the CD4+ T-cell analyzer was out of order or did not have reagents. In such cases, the recorded action was that CD4_ T-cell test had been ordered. In a few cases, clinicians’ perception was that the CDSS alert was incorrectly raised due to errors in the data (e.g. an incorrect CD4+ T-cell value entered in the EHR).
Table 6.2: Characteristics of HIV patients receiving HIV care at 13 HIV clinics in Siaya County, Kenya in 2013

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>Total</td>
<td>41062</td>
<td>19662</td>
<td>21400</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 years</td>
<td>3392</td>
<td>8.3(8 - 8.5)</td>
<td>1718</td>
</tr>
<tr>
<td>15-24 years</td>
<td>7462</td>
<td>18.2(17.8 - 18.5)</td>
<td>3899</td>
</tr>
<tr>
<td>25-49 years</td>
<td>26013</td>
<td>63.4(62.9 - 63.8)</td>
<td>12264</td>
</tr>
<tr>
<td>50+ years</td>
<td>4195</td>
<td>10.2(9.9 - 10.5)</td>
<td>1781</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14337</td>
<td>34.9(34.5 - 35.4)</td>
<td>6676</td>
</tr>
<tr>
<td>Female</td>
<td>26725</td>
<td>65.1(64.6 - 65.5)</td>
<td>12986</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>21972</td>
<td>53.5(53 - 54)</td>
<td>10759</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>3254</td>
<td>7.9(7.7 - 8.2)</td>
<td>1427</td>
</tr>
<tr>
<td>Widow</td>
<td>8007</td>
<td>19.5(19.1 - 19.9)</td>
<td>3791</td>
</tr>
<tr>
<td>Single</td>
<td>7829</td>
<td>19.1(18.7 - 19.4)</td>
<td>3685</td>
</tr>
<tr>
<td>Baseline CD4 category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;350</td>
<td>35583</td>
<td>86.7(86.3 - 87)</td>
<td>16893</td>
</tr>
<tr>
<td>350-500</td>
<td>4993</td>
<td>12.2(11.8 - 12.5)</td>
<td>2489</td>
</tr>
<tr>
<td>&gt;500</td>
<td>486</td>
<td>1.2(1.1 - 1.3)</td>
<td>280</td>
</tr>
<tr>
<td>WHO stage at enrolment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO I</td>
<td>10877</td>
<td>26.5(26.1 - 26.9)</td>
<td>5936</td>
</tr>
<tr>
<td>WHO II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO II</td>
<td>12322</td>
<td>30 (29.6 - 30.5)</td>
<td>6295</td>
</tr>
<tr>
<td>-------------</td>
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<td>-----------------</td>
<td>------</td>
</tr>
<tr>
<td>WHO III</td>
<td>16710</td>
<td>40.7 (40.2 - 41.2)</td>
<td>6950</td>
</tr>
<tr>
<td>WHO IV</td>
<td>1153</td>
<td>2.8 (2.6 - 3)</td>
<td>480</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfer out</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>36295</td>
<td>88.4 (88.1 - 88.7)</td>
<td>17289</td>
<td>87.9 (87.5 - 88.4)</td>
<td>19006</td>
<td>88.8 (88.4 - 89.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>4767</td>
<td>11.6 (11.3 - 11.9)</td>
<td>2373</td>
<td>12.1 (11.6 - 12.5)</td>
<td>2394</td>
<td>11.2 (10.8 - 11.6)</td>
</tr>
</tbody>
</table>

| First-line regimen |            |            |      |                  |      |                   |
| Nevirapine (NVP)   | 18534      | 85.7 (85.2 - 86.1) | 9097  | 86.3 (85.7 - 87)  | 9438  | 85 (84.4 - 85.7)  |
| Efavirenz (EFV)    | 2986       | 13.8 (13.3 - 14.3) | 1399  | 13.3 (12.6 - 13.9) | 1588  | 14.3 (13.7 - 15)  |
| Other              | 118        | 0.5 (0.4 - 0.6)   | 45    | 0.4 (0.3 - 0.5)   | 74    | 0.7 (0.5 - 0.8)   |

| ART adherence at last visit |            |            |      |                  |      |                   |
| Satisfactory           | 21604      | 99.8 (99.8-99.9) | 10525 | 99.9 (99.8-99.9)  | 11079 | 99.8 (99.7-99.9)  |
| Unsatisfactory         | 35         | 0.2 (0.1-0.2)   | 15    | 0.1 (0.1-0.2)    | 20    | 0.2 (0.1-0.3)    |
Table 6.3: Association between CDSS alerts and action on treatment failure and ART initiation among HIV patients in Siaya County, Kenya in 2013

<table>
<thead>
<tr>
<th>Variable</th>
<th>Label</th>
<th>Action on treatment failure *</th>
<th>Action on eligible patients not initiated on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted odds ratio (95% confidence interval)</td>
<td>Adjusted odds ratio (95% confidence interval)</td>
<td>Unadjusted odds ratio (95% confidence interval)</td>
</tr>
<tr>
<td>Site status</td>
<td>Control</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>2.91(2.43 - 3.49)</td>
<td>2.96(2.45 - 3.56)</td>
</tr>
<tr>
<td>Age group, years</td>
<td>&lt;15 years</td>
<td>1.17(0.83 - 1.65)</td>
<td>1.10(0.77 - 1.57)</td>
</tr>
<tr>
<td></td>
<td>15-24 years</td>
<td>1.52(1.05 - 2.19)</td>
<td>1.62(1.1 - 2.38)</td>
</tr>
<tr>
<td></td>
<td>25-49 years</td>
<td>1.40(1.09 - 1.80)</td>
<td>1.51(1.17 - 1.97)</td>
</tr>
<tr>
<td></td>
<td>50+ years</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1.10(0.93 - 1.32)</td>
<td>1.12(0.93 - 1.35)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>1.39(1.11 - 1.76)</td>
<td>0.46(0.15 - 1.39)</td>
</tr>
<tr>
<td></td>
<td>Divorced/Separated</td>
<td>1.16(0.72 - 1.87)</td>
<td>1.32(0.24 - 7.37)</td>
</tr>
<tr>
<td></td>
<td>Single</td>
<td>1.26(0.94 - 1.69)</td>
<td>0.55(0.18 - 1.65)</td>
</tr>
<tr>
<td></td>
<td>Widow</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CD4 category</td>
<td>&lt;350</td>
<td>2.5(1.59 - 3.93)</td>
<td>1.47(0.71 - 3.06)</td>
</tr>
</tbody>
</table>
### WHO stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>350-500</th>
<th>&gt;500</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO I</td>
<td>1.65(0.94 - 2.91)</td>
<td>1.03(0.28-3.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>WHO II</td>
<td>1.71(1.33 - 2.2)</td>
<td>1.68(1.29 - 2.19)</td>
<td>1.0</td>
</tr>
<tr>
<td>WHO III</td>
<td>1.76(1.38 - 2.24)</td>
<td>1.5(1.16 - 1.95)</td>
<td>1.0</td>
</tr>
<tr>
<td>WHO IV</td>
<td>1.64(0.84 - 3.19)</td>
<td>1.27(0.61 - 2.63)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### First-line regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>350-500</th>
<th>&gt;500</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>1.29(0.47 - 3.58)</td>
<td>0.42(0.12 - 1.55)</td>
<td>1.0</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1.13(0.39 - 3.25)</td>
<td>0.56(0.14 - 2.24)</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### ART adherence

<table>
<thead>
<tr>
<th>Adherence</th>
<th>1.53(0.14 - 16.9)</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory</td>
<td>1.53(0.14 - 16.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* - Immunological treatment failure occurs when there is sub-optimal response by the immune system to ART.
Figure 6.2: Time from immunological treatment failure to appropriate action among HIV patients receiving ART in Siaya County.

Figure 6.3: Time from ART initiation to first CD4+ T-cell measurements among patients at Siaya County in 2013.
6.4 Discussion

The results of this study provide compelling evidence that CDSS support clinicians in timely detection and appropriate action on HIV treatment failure in conformity with HIV treatment guidelines. The likelihood of clinicians taking appropriate action on immunological treatment alerts as recommended in the treatment guidelines due to decision support was 2.96 times the likelihood without decision support. Additionally, there was a 72% relative reduction in the median time taken from detection of conditions for treatment failure to appropriate action as well as timely performance of CD4+ T-cell measurements as recommended in the national HIV treatment guidelines. Timely detection and action on HIV treatment failure can substantially reduce the risk of disease progression, drug resistance and even death (19). Further, early actions such as ART adherence counseling or repeat/confirmatory CD4+ T-cell count can save the cost of treatment through the avoidance of the more expensive second line regimens that are also more complex to administer and monitor. Second line drugs cost nearly 40% more than the cost of first line drugs; for example, the annual cost of standard first-line ART for an adult patient in Kenya in 2012 was $248 compared to $340 for second-line regimen (28).

Our study also showed that CDSS improved timely performance of CD4+ T-cell measurements, which is a critical quality-of-care indicator for immunological response to treatment. There was no significant association between the use of CDSS and initiation of ART among eligible patients. This is consistent with findings by Oluoch et al. which attributed lack of association to factors such as provider practice (clinician’s behavior) and the patient’s own readiness to initiate ART (29). The overall improvement in quality of care demonstrated in our study is consistent with many studies included in the systematic reviews by Roshonov et al. and Oluoch et al. (12;18) and adds to the limited number of studies on CDSS conducted in resource-constrained settings such as that by Were et al. (30). The cluster randomized design of our study and the large sample size from multiple study sites minimized bias and improved the precision of estimates. Performing both CC and MI was reassuring as the results from the two analyses were comparable with only slight variations in p-values.

It is worth noting that although the intervention was very effective there is still a large room (~45%) for improvement in the actions taken on treatment failure. Based on studies conducted in sub-Saharan Africa which estimate that 15 – 25% of HIV patients receiving ART experience immunological treatment failure (3-6) the implication of lack of action on the alerts in Kenya where about 650,000 HIV patients were receiving ART as of March 2014 (31) is that at least 59,000 individuals could be experiencing immunological treatment failure with no action taken. Our study provided strong evidence that CDSS can significantly reduce this number but there should be adequate capacity to act on the recommendations of the CDSS, including laboratory capacity to ensure timely conduct of CD4+ T-cell tests and optimal number of clinical staff with skills to act appropriately on immunological treatment failure.

The findings from our study are subject to some limitations. Due to the high number of patients attending clinics with limited health workers, some actions may have been performed (e.g. CD4 tests) but not recorded in the EHR. This was particularly evident in control sites where fewer alerts on overdue CD4 were noted despite regular supervision at all study sites to ensure high quality of data. This could be an indication that CDSS alerts remind clinicians to record missing CD4 results. In addition, clinical and nursing officers were frequently transferred to and from the study clinics thereby introducing new health workers with no knowledge of the study. Ongoing training of clinical staff by the study team minimized the effect of such transfers. None of the staff was transferred from one study site to another thereby eliminating any “cross over effect”. Randomization did not uniformly assign patients by severity...
of illness (WHO clinical stage). To correct for this, we adjusted for WHO stage in the multivariate analysis. New WHO HIV treatment guidelines launched in July 2013 recommend the use of viral load test for monitoring patients’ response to HIV treatment (32) and Kenya is currently in the process of transitioning from immunological to virological monitoring of patients. This announcement came in the last six months of the study and had not taken effect by January 2014 when our data collection ended. A few countries in SSA are beginning to roll-out routine viral load monitoring, but the operationalization and feasibility of this still requires close monitoring and evaluation.

6.5 Conclusion:

Our study showed that CDSS improved the likelihood of timely and appropriate action on immunological treatment failure among HIV patients in resource limited settings. We expect that the strong effects demonstrated in this study will be generalizable to improvement of virological monitoring of patients receiving ART once CDSS has implemented the new WHO HIV treatment guidelines.

Acknowledgements:
The authors would like to acknowledge the KEMRI Director and his staff for the approval of this study and for reviewing and clearing the manuscript. We would also like to thank all staff at the 13 clinics in Siaya County that supported the data collection for this study.

Trial Registration: This trial is registered at clinicaltrials.org (ID: NCT01634802)
Reference List


### Appendix 6.1:

**WHO Clinical Staging of HIV/AIDS in Adults and Adolescents**

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Stage 1</strong></td>
</tr>
<tr>
<td>1. Asymptomatic</td>
</tr>
<tr>
<td>2. Persistent generalized lymphadenopathy</td>
</tr>
<tr>
<td><strong>Clinical Stage 2</strong></td>
</tr>
<tr>
<td>1. Moderate unexplained weight loss (&lt;10% of presumed or measured body weight)</td>
</tr>
<tr>
<td>2. Minor mucocutaneous manifestations (seborrheic dermatitis, papular pruritic eruptions, fungal nail infections, recurrent oral ulcerations, angular cheilitis)</td>
</tr>
<tr>
<td>3. Herpes zoster</td>
</tr>
<tr>
<td>4. Recurrent upper respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis)</td>
</tr>
<tr>
<td><strong>Clinical Stage 3</strong></td>
</tr>
<tr>
<td>1. Unexplained severe weight loss (over 10% of presumed or measured body weight)</td>
</tr>
<tr>
<td>2. Unexplained chronic diarrhea for longer than one month</td>
</tr>
<tr>
<td>3. Unexplained persistent fever (intermittent or constant for longer than one month)</td>
</tr>
<tr>
<td>4. Persistent oral candidiasis</td>
</tr>
<tr>
<td>5. Oral hairy leukoplakia</td>
</tr>
<tr>
<td>6. Pulmonary tuberculosis</td>
</tr>
<tr>
<td>7. Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)</td>
</tr>
<tr>
<td>8. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis</td>
</tr>
<tr>
<td>9. Unexplained anemia (below 8g/dl), neutropenia (below 0.5 x 10⁹/l) and/or chronic thrombocytopenia (below 50 x 10⁹/l)</td>
</tr>
<tr>
<td><strong>Clinical Stage 4</strong></td>
</tr>
<tr>
<td><strong>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations</strong></td>
</tr>
<tr>
<td>1. HIV wasting syndrome</td>
</tr>
<tr>
<td>2. Pneumocystis jiroveci pneumonia (PCP)</td>
</tr>
<tr>
<td>3. Recurrent severe bacterial pneumonia (&gt;2 episodes within 1 year)</td>
</tr>
<tr>
<td>4. Cryptococcal meningitis</td>
</tr>
<tr>
<td>5. Toxoplasmosis of the brain</td>
</tr>
<tr>
<td>6. Chronic oro-labial, genital or ano-rectal herpes simplex infection for &gt; 1 month</td>
</tr>
<tr>
<td>7. Kaposis Sarcoma</td>
</tr>
<tr>
<td>8. HIV encephalopathy</td>
</tr>
<tr>
<td>9. Extra-pulmonary tuberculosis</td>
</tr>
<tr>
<td><strong>Conditions where confirmatory diagnosis testing is necessary:</strong></td>
</tr>
<tr>
<td>1. Cryptosporidiosis, with diarrhea &gt; 1 month</td>
</tr>
<tr>
<td>2. Isosporiasis</td>
</tr>
<tr>
<td>3. Cryptococcosis (extra-pulmonary)</td>
</tr>
<tr>
<td>4. Disseminated non-tuberculosis mycobacterial infection</td>
</tr>
<tr>
<td>5. Cytomegalovirus (CMV) retinitis or infection of the organs (other than liver, spleen, or lymph nodes)</td>
</tr>
<tr>
<td>6. Progressive multifocal leucoencephalopathy (PML)</td>
</tr>
<tr>
<td>7. Any disseminated mycosis (e.g. histoplasmosis, coccidioidomycosis)</td>
</tr>
<tr>
<td>8. Candidiasis of the oesophagus or airways</td>
</tr>
<tr>
<td>9. Non-typhoid salmonella (NTS) sepsicaemia</td>
</tr>
<tr>
<td>10. Lymphoma cerebral or B cell non-Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>11. Invasive cervical cancer</td>
</tr>
<tr>
<td>12. Visceral leishmaniasis</td>
</tr>
<tr>
<td>13. Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy</td>
</tr>
</tbody>
</table>
Chapter 7

A structured approach to recording AIDS-defining illnesses in Kenya: A SNOMED CT based solution

*Submitted for publication*

Tom Oluoch
Nicolette de Keizer
Patrick Langat
Irene Alaska
Kenneth Ochieng
Nicky Okeyo
Daniel Kwaro
Ronald Cornet
Co-authors’ contribution

T. Oluoch, N. de Keizer and R. Cornet conceptualized and designed the study. I. Alaska and D. Kwaro contributed to the clinical components of the study and manuscript review. P. Langat and N. Okeyo provided oversight to the data management team that conducted the chart abstraction, focus group discussion (FGD) and overall data cleaning. K. Ochieng did the programming in OpenMRS, including developing the user interface. All co-authors were involved in interpreting the results. T. Oluoch, N. de Keizer and R. Cornet drafted and revised the manuscript. All authors edited and reviewed the manuscript and gave their final approval for submission to the journal.
Abstract:

Introduction
Several studies conducted in sub-Saharan Africa (SSA) have shown that routine clinical data in HIV clinics often have errors. Key data elements such as diagnosis of AIDS-defining illnesses (ADIs) are often missing, resulting in incorrect inference of WHO clinical staging, an indicator of progression of HIV infection. This negatively impacts the quality of care provided.

Methods:
We used a structured framework to derive a reference set of concepts and terms used to describe ADIs. The four sources used were: (i) CDC/Accenture list of opportunistic infections (ii) SNOMED Clinical Terms (SNOMED CT) (iii) Focus Group Discussion (FGD) among clinicians and nurses attending to patients at a referral provincial hospital in western Kenya, and (iv) chart abstraction from the Maternal Child Health (MCH) and HIV clinics at the same hospital. Using the January 2014 release of SNOMED CT, concepts were retrieved that matched terms abstracted from approach iii & iv, and the content coverage assessed. Post-coordination matching was applied when needed.

Results:
The final reference set had 1,054 unique ADI concepts which were described by 1,860 unique terms. Content coverage of SNOMED CT was high (99.9% with pre-coordinated concepts; 100% with post-coordination). The resulting reference set for ADIs was implemented as the interface terminology on OpenMRS data entry forms.

Conclusion:
Different sources demonstrate complementarity in the collection of concepts and terms for an interface terminology. SNOMED CT provides a high coverage in the domain of ADIs. Further work is needed to evaluate the effect of the interface terminology on data quality and quality of care.
7.1 Introduction

AIDS-Defining opportunistic Illnesses (ADIs), defined as illnesses that occur with more severity and higher frequency among persons with HIV, remain the main course of morbidity and mortality among HIV-infected persons (1;2). Although several studies show a decline in incidence of individual ADIs such as tuberculosis, Pneumocystis pneumonia and Kaposi sarcoma since the introduction of anti-retroviral therapy (ART) (3;4), mortality associated with ADIs remains high. Sub-Saharan Africa (SSA), which is home to nearly two-thirds of the world’s 33.6 million people living with HIV, also has the highest rates of HIV-ADI co-infection (5). The US Centers for Disease Control and Prevention (CDC) and the World Health Organisation (WHO) have released guidelines for prevention and treatment of ADIs, intended for use by healthcare providers and policy makers (6;7). WHO classifies ADIs into four clinical stages indicative of HIV disease progression to help clinicians in resource-limited settings (mainly in Africa and Asia) with no immediate access to CD4 T-cell count testing to make decisions on ART eligibility (8).

Many studies conducted in SSA have shown that routine clinical data often have errors and in several cases missing key data elements such as diagnosis of ADIs (9-11). Poor recording or incorrect inference of WHO clinical staging based on the ADIs can lead to under or over-treatment of patients. A majority of clinics providing HIV care and treatment in SSA use a fixed list of coarse-grained ADIs to perform clinical staging of HIV-infection as recommended by WHO (8). Kiragga et al estimate that ADIs in clinical settings are under-reported by up to 67% in HIV clinics in Uganda (10). The unstructured nature of free-text recording of diagnoses and the limited list of preselected common ADIs from which clinicians can select diagnoses limits data completeness and re-usability e.g. in decision support or statistical analysis as the diagnoses are not uniquely defined and identified with a code (10;12). Additionally, in busy clinics with over-worked health workers, ADIs are rarely recorded with a fine granularity including more specific disease sub-types. Lack of granular information on diagnosis may influence continuity of treatment given.

Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) in Kisumu county, western Kenya has two busy HIV clinics where more than 7,000 patients receive care and treatment. The hospital does not have a standardized way of documenting signs, symptoms and disorders during patient visits. This potentially impacts the quality of data recorded, inference of WHO clinical staging as well as continuity of care for patients. In order to address this problem, we propose to standardize the recording of ADIs using a standard terminology. A terminology system such as SNOMED Clinical Terms (SNOMED CT) can contribute to data accuracy and re-use through concept-based definition of diagnoses and coded storage of data (13).

This study describes a structured approach to derive a comprehensive set of ADI concepts based on SNOMED CT and evaluates SNOMED CT’s content coverage for ADIs in a provincial referral hospital in Kenya. The resultant set of concepts will be integrated into Electronic Medical Record (EMR) systems and implemented as an interface terminology in OpenMRS at the JOOTRH providing clinicians with a standardized tool for fine-grained recording of ADIs and automated inference of WHO clinical staging.
7.2 Background

7.2.1 WHO Clinical Staging and ART Eligibility

The WHO clinical staging uses clinical presentation of patients to categorize HIV infection into 4 stages based on the severity of ADIs and prognosis. The stage reflects progression of HIV infection from asymptomatic to conditions where presumptive diagnoses can be made on the basis of clinical presentation or simple investigations (8). Clinical staging is progressive, meaning that when a patient has recovered from a condition defined in a higher stage, they retain the higher clinical stage and can never be classified at a lower stage. Patients with stage I and II HIV infection present with (or have a history of) conditions such as minor skin diseases and upper respiratory tract infections, which are indicative of early HIV infection. WHO clinical stages III and IV, which are indicative of advanced HIV disease, may manifest as one or more illnesses such as severe bacterial infection, extra-pulmonary tuberculosis and non-Hodgkin lymphoma. WHO recommends initiation of ART for patients who have stage III or stage IV conditions (8).

The Kenyan Ministry of Health (MOH) HIV care and treatment guidelines (14), which are adapted from the WHO guidelines, recommend that all HIV-infected pregnant women receive ART, irrespective of their immunological or clinical indication of opportunistic infections associated with HIV (7).

7.2.2 SNOMED CT

SNOMED CT is an international logic-based, controlled vocabulary used in clinical care that amongst other areas includes terms for diagnostic concepts (15). SNOMED CT enables meaning-based retrieval of clinical information from electronic health records (EHR) and is able to express finer-grained concepts than classification systems such as ICD-10. For this study, we used the January 2014 release of SNOMED CT which had 298,581 active concepts associated with 781,878 active descriptions. The concepts are interrelated by 896,942 active relationships which can be hierarchical (Is-A relationship) or non-hierarchical (e.g. “associated morphology” or “finding site”). A SNOMED CT reference set provides a mechanism to group concepts and/or descriptions for a common goal (such as diagnosis concepts for AIDS defining illnesses).

Rosenbloom et al describe an interface terminology as a systematic collection of health-care phrases or terms that support clinicians’ entry of patient-related information into computer programs and decision tools (16). Interface terminologies also support the display of computer-stored patient information to clinical users in simple human-readable format. The use of a SNOMED CT based terminology on the user interface of an EMR supports efficient selection of terms during data entry based on uniquely coded concepts and promotes data re-use in decision support and statistical analysis.

7.3 Methods

7.3.1 Study setting

The JOOTRH provides ambulatory HIV care and treatment services to over 7,000 active patients, of whom about 4,800 are receiving ART. The services are provided within the Maternal and Child Health (MCH), the HIV clinic/Patient Support Centre (PSC) and the Integrated Tuberculosis clinic. The three
clinics in the hospital use a hybrid system of paper records and EMR to manage patient data; the EMR system is currently under staged deployment and is expected to replace the paper records by the end of 2014. The study was conducted at the HIV/PSC clinic and the MCH clinic which includes the Ante-Natal Care (ANC) clinic.

7.3.2 Study participants

We extracted free-text data used to describe diagnoses, signs and symptoms from paper-based clinical notes for all HIV-positive patients receiving care and treatment services at the HIV/PSC as well as HIV-positive pregnant women presenting for antenatal care or at the labor and delivery room during the months of February and March 2014, and receiving Antiretroviral Therapy (ART). We also conducted a Focus Group Discussion (FGD) among clinicians and nurses who attend to patients visiting the MCH and HIV/PSC clinics.

7.3.3 Review of term-based ADI recording

A trained clinician (clinical officer) extracted terms for diagnoses, signs and symptoms recorded in the patient charts to determine the terms used to document ADIs at the ANC and HIV/PSC. Data were retrieved from the two clinics to ensure comprehensive coverage of terms used to describe ADIs. Although terms for diagnoses, signs and symptoms were retrieved from the charts, we only included in the analysis those that matched SNOMED CT “disorder” concepts as described later.

7.3.4 Deriving ADI reference set

Based on a framework developed by Bakhshi-Raiez et al (17), we derived the reference set of ADI concepts through a multi-step approach. The first three steps describe how the ADI reference set was derived as shown in Figure 7.1. In the first step, concept-based subsets of ADIs from SNOMED CT and Accenture/CDC (described below) were merged. The CliniClue Xplore browser (18) and NICTIZ terminology explorer (19) were used to explore the concepts. The second step entailed extraction of term-based concepts from patient charts and Focus Group Discussions. In step 3, the concept-based and term-based concepts were merged.

Step 1: Processing concept-based ADI subsets

(a) Accenture/CDC subset: The US Centers for Disease Control and Prevention (CDC) derived a list of opportunistic infections considered to be AIDS defining illnesses (6). CDC and Accenture mapped the diagnosis and organism concepts on to SNOMED CT to come up with a hierarchical set of SNOMED CT-based concepts stored in the Web Ontology Language (OWL) format (20). The Accenture/CDC subset contains 907 concepts and 1,528 associated descriptions for ADIs.

(b) SNOMED CT subset: We used structured query language (SQL) commands to select concepts and descriptions associated with ADIs from an instance of the January 2014 release of SNOMED CT which was stored in a MySQL database. The SQL commands were based on the conditions described below:

- Concepts described by terms including “assoc” and (“AIDS” or “HIV”)
- Concepts linked by the relationship “associated with” to the concept “HIV infection”
- All subtypes (descendants) of the above selected concepts
- The active descriptions of the resulting concepts in SNOMED CT
The SQL queries used to retrieve the data are in Appendix 7.1. Since all patients seen in the study clinics had HIV, those supertypes of concepts were retrieved that did not include the phrase “Associated with AIDS”. For example: *Pneumococcal Pneumonia associated with AIDS* (concept ID = 420787001) was replaced with the parent concept *Pneumococcal Pneumonia* (concept ID = 233607000).

The two ADI subsets described in steps (a) and (b) above were merged into subset A as shown in Figure 7.1, sorted by SNOMED CT concept ID and all duplicate concepts and terms deleted.

**Step 2: Deriving term-based concepts**

(a) **Free text abstraction**

Two clinical officers reviewed free-text records from 583 initial patient visits and 762 follow-up visits for the same patients who visited the JOOTRH ANC and HIV/PSC clinics in the months of February and March 2014 and abstracted terms used to describe ADIs at the clinic. The free-text terms were extracted from paper-based patient records as well as those entered in the OpenMRS EMR. Terms and description IDs from SNOMED CT that matched the free-text terms were retrieved by a medical informatician with SNOMED CT expertise (TO). These concepts and the terms describing them were stored as subset B (Figure 7.1).

(b) **Focus Group Discussion**

In this step, a focus group discussion (FGD) was held involving clinicians who attend to patients at the ANC and HIV/PSC clinics. A separate FGD was conducted among nurses working at the same clinics. All descriptions for the concepts from subset A were made available to the clinicians prior to the start of the FGD. Clinicians’ and nurses’ knowledge was sought on the most common ADIs in their setting (JOOTRH). Using local terms, they listed as many ADIs as they could in addition to the concepts and terms included in subset A. Clinicians and nurses were further asked what factors they consider in determining whether the symptoms and signs are suggestive of an ADI. Terms and description IDs from SNOMED CT that matched terms used for ADI diagnoses in the FGD were retrieved by the same medical informatician (TO).

The terms and concepts derived through abstraction of data from the MCH/PSC records and the FGD were merged into subset B and duplicates removed (see Figure 7.1). Concepts were retrieved from SNOMED CT based on the “exact match” and if needed, by post-coordination. The example below shows how we derived a post-coordinated concept *oropharyngeal candidiasis* which is not in SNOMED CT. CDC describes *oropharyngeal candidiasis* as *candidiasis that develops in the throat or mouth* (21).

Candidiasis (78048006) : finding site (363698007) = Mouth and/or pharynx structures (312533001).

**Step 3: Merging the subsets**

In the final step, all derived concepts (subsets A and B) and their descriptions were merged into a single subset C and all duplicate concepts and descriptions deleted.
Step 4: SNOMED CT subset extension

If terms could not be matched with SNOMED CT concepts and descriptions, these terms were presented to a team of clinicians and informaticians with expertise in SNOMED CT for review. They determined whether these could be considered as local extensions of SNOMED CT through post-coordination of concepts or as entirely new concepts or descriptions.

Step 5: Constraining the ADI subset

Several non-ADI concepts were deleted from the term-based subsets. Although these non-ADIs were common co-infections that HIV patients attending the clinics at JOOTRH present with, they were not considered for implementation of the interface terminology. Such non-ADI concepts included malaria (concept ID = 61462000) and urinary tract infection (concept ID = 68566005).

7.3.5 Implementation of the interface terminology

The resulting concept subset and description subset from the above steps were represented in the OpenMRS concept dictionary and implemented as the interface terminology on OpenMRS data entry forms to improve ease and accuracy of recording of ADIs. A separate set of non-ADI concepts representing common co-infections or signs, symptoms among patients seeking HIV treatment at JOOTRH was also created from the chart review and FGD for the purpose of presentation on the user interface. Subsetting the concepts into ADI and non-ADI disorders for the purpose of presentation on the user interface provides clinicians quick access to shorter lists of relevant diagnosis concepts to choose from. The ADI concepts were presented on the user interface as a dropdown menu with autocomplete/autosuggest textbox feature derived using a list builder. A 'more details' button is displayed for each of the ADIs selected for a particular patient. Clicking on this button allows the selection of qualifiers of a particular diagnosis.

The patients’ WHO staging is automatically inferred based on the recorded ADI concept. To accomplish this, the ADI concept is matched with the corresponding WHO stage as defined in the HIV treatment guidelines (8;14). The WHO clinical staging list showing the ADI concepts and corresponding WHO clinical stage is in Appendix 7.2 (8).

7.3.6 Ethical considerations

The study was approved by the Associate Director for Science at the Center for Global Health of the US Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI) institutional review board. The women whose data were included in the study consented to the use of their data for clinical care and research studies taking place at the ANC clinic. As the study subjects were considered a vulnerable population (HIV-positive pregnant women), the study team ensured that the individual patient data were de-identified and their privacy and confidentiality maintained in line with the KEMRI guidelines on research ethics.
7.4 Results

A total of 1,104 ADI concepts were derived from the four data sources. The final reference set had 1,054 unique concepts after deleting 50 duplicate concepts. The 1,054 unique concepts were described by 1,860 unique terms. Figure 7.1 shows the number of terms and concepts used to describe ADIs in each subset.

Figure 7.1: Derivation of terms and concepts used to describe ADI from concept-based and term-based sources.

7.4.1 Concept-based terms (CDC ADI and SNOMED CT Subsets)

The CDC/Accenture ADI subset had 907 unique disorder concepts described by 1,528 terms. For the SNOMED CT subset, the first query (concepts described by terms including "assoc" and ("AIDS" or "HIV")) yielded 102 concepts while the second query (concepts linked by the relationship "associated with" (ID=47429007) to the concept "HIV infection" (ID=86406008)) resulted in 107 unique concepts. Some 102 duplicate concepts between the two queries were deleted, resulting in 105 unique concepts. Finally, the subtype children of the resulting concepts were derived using the fourth query. Where relevant, these concepts were replaced by their supertype concept for which the description did not contain "associated with AIDS". For the resulting 110 concepts, 254 terms together with their description ID were retrieved from SNOMED CT.

7.4.2 Term-based concepts (Abstraction from MCH and PSC, and Focus Group Discussions)

A total of 87 ADI concepts were derived from the term-based subset i.e. those abstracted from the paper records of patients attending the MCH clinic and PSC, and from the FGD. The concepts were described using 157 terms.
7.4.3 Content coverage

The overall content coverage was 99.9% with pre-coordinated concepts and 100% with post-coordination. All but two term-based concepts from the chart abstraction at the MCH and PSC, as well as the FGDs matched the SNOMED CT concepts. The two concepts that required post-coordination were: (i) Oropharyngeal candidiasis, and (ii) Genital ulcer disease. Oropharyngeal candidiasis was post-coordinated as: Candidiasis (78048006) : finding site (363698007) = Mouth and/or pharynx structures (312533001). Genital ulcer disease was post-coordinated as: Ulcer (429040005) : finding site (363698007) = Structure of genital organ (700037000).

7.4.4 Interface terminology implementation

The implementation of the interface terminology includes 1,860 terms describing 1,054 unique concepts. The implementation included qualifiers such as severity (e.g. “mild”, “moderate” or “severe”), onset (e.g. “sudden” or “gradual”) and laterality which describes the side of the body that is infected (e.g. right middle zone pneumonia indicative that the infection is in the right middle lobe of the lung). Defining characteristics which include causative agent were implicit to the interface terminology, allowing more specific types of diagnosis to be selected (e.g. for “pneumococcal pneumonia” where “pneumococcus” is the causative agent). Additional context information that can be selected is the type of diagnosis, i.e. presumptive (working), differential or final diagnosis (See Figure 7.2).

Figure 7.2: A screen-shot of a data entry form using ADI reference set
7.5 Discussion

More than 1,000 ADI concepts described by nearly 1,900 terms were derived from four data sources using a well-structured approach based on an earlier published framework for developing interface terminology reference sets (17). While most concepts were described by one term, some of the concepts were described using as many as 9 terms which provide a wide variety of relevant synonyms that include locally used terms from which clinicians can make selections to accurately describe diagnoses. Content coverage was high; consistent with the study by Rosenbloom et al (22). In our study, all but two concepts generated from the term-based sources matched SNOMED CT concepts.

Although signs and symptoms were included in the data abstracted from the MCH and PSC, as well as the FGD, we did not include them in the final reference set since they had a very broad scope and some were not associated with HIV infection. It is important to note that the WHO clinical staging list includes some signs and symptoms such as fever (concept ID = 421154002) together with ‘real’ ADIs used to determine the progression of HIV infection based on clinical presentation of the patient (8) (see Appendix 7.2). These will be added to the local concept dictionary through dynamic updates to support automated inferencing of WHO clinical staging. The ADI list of concepts will be shared with Columbia University that maintains the concept dictionary for OpenMRS users. It will also be shared with the International Health Terminology Standards Development Organization (IHTSDO) that maintains SNOMED CT for distribution to its members and affiliates. Access to the reference set can be gained by contacting IHTSDO.

An observation of the term-based data abstracted from the MCH clinic and PSC, as well as data recorded from the FGDs showed a number of spelling mistakes. This shows that lack of a structured list of ADIs with a rich selection of terms contributes to poor data quality on diagnoses entered in EMR systems, as observed elsewhere (12). The implementation of an interface terminology with the ADIs selected from a comprehensive reference set that includes child and parent concepts of key disorders will enhance the quality of data recorded leading to appropriate decisions on clinical care. Additionally, enhanced decision support through automated inference of WHO clinical stage based on the recorded ADIs will ensure that patients get appropriate treatment determined by the accurate recording of progression of HIV infection. The study benefited from data collection from a busy referral hospital that provides HIV care and treatment to a large number of patients with diverse conditions hence a broad coverage of terms used to describe ADIs. Furthermore, the use of chart abstraction and FGDs enabled the study team to collect context-specific terms that are most appropriate for local use at JOOTRH but may also be broadly used in similar contexts in low-resource settings.

Our study had a few limitations. The chart abstraction was conducted over a two-month period and this may not be long enough to provide the breadth of data required. The effect of the short data collection period was minimized since this is a high-volume hospital with diverse patients. Incorrect spellings and use of ADI terms that were not specific enough, made matching SNOMED CT concepts difficult. Consultation with the clinicians helped resolve the errors and all the terms were matched. Additionally, the EMR implementation has a provision for dynamic update of concepts which may be missing from the current list or those that will be derived through post-coordination of new and existing terms.

7.6 Conclusion

We described a structured approach to deriving an ADI reference set based on SNOMED CT and the implementation of an interface terminology for OpenMRS at a busy provincial referral hospital in a
resource-constrained setting. Use of different sources demonstrates complementarity in the collection of concepts and terms for an interface terminology. SNOMED CT provides a high coverage in the domain of ADIs. The context-specific reference set will support improved recording of high quality data ensuring completeness and reusability. Further work is needed to evaluate the effectiveness of the interface terminology on data quality and quality of care.

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Conflicts of interest:
Authors are members of the Technical Committee (RC) and Quality Assurance Committee (NdK) of the International Health Terminology Standards Development Organization (IHTSDO), which publishes SNOMED CT. Their positions at the IHTSDO, however, had no bearing on the research study or results.
Reference List


(8) World Health Organization. WHO Case Definitions of HIV For Surveillance and Revised Clinical Staging and Immunological Classification of HIV-related Disease in Adults and Children. 2006.


(19) NICTIZ. Terminologiecentrum Nictiz. NICTIZ 2014 October 10 Available from: URL: http://terminologie.nictiz.nl/art-decor/snomed-ct

(20) US Centers for Disease Control and Prevention, Accenture. Unpublished list of AIDS Defining Illnesses. 6-6-2012.


Appendix 7.1:

SQL Queries for retrieval of ADI concept IDs for ADIs from SNOMED CT database

We used the queries below to retrieve the relevant ADI concepts and descriptions:

(i) **Concepts described by terms including “assoc” and (“AIDS” or “HIV”)**

```sql
CREATE VIEW c1 AS
    SELECT c201401.Id, c201401.active, c201401.definitionStatusld, d201401.conceptID, d201401.typeId, d201401.term
    FROM c201401
    JOIN d201401 ON c201401.Id = d201401.conceptId
    WHERE c201401.active =1
    AND d201401.active =1
    AND (d201401.term LIKE '%AIDS%' OR d201401.term LIKE '%HIV%')
    AND d201401.term LIKE '%assoc%'
(n = 102 unique concepts)
```

(ii) **Concepts linked by the relationship “associated with” (Id=47429007) to the concept “HIV Infection” (Id=86406008)**

```sql
CREATE VIEW `c2` AS
    select `sourceconcept`.`Id` AS `conceptId`
    FROM (((`c201401` `sourceconcept` join `r201401` on ((`sourceconcept`.`Id` = `r201401`.`sourceId`)))
    JOIN `transitiveclosure_20140131` `t1` ON ((`r201401`.`destinationId` = `t1`.`SubtypeId`)))
    JOIN `transitiveclosure_20140131` `t2` ON ((`t2`.`SubtypeId` = `r201401`.`typeId`))
    WHERE ((`sourceconcept`.`active` = 1) and (`r201401`.`active` = 1) AND (`t1`.`SupertypeId` = 86406008) AND (`t2`.`SupertypeId` = 47429007))
    (n = 105 unique concepts)
```

(iii) **Merging the two views c1 and c2 into a new one c3**

```sql
CREATE VIEW `c3` AS
    SELECT `c1`.`Id` AS `conceptId`
    FROM `c1` union select `c2`.`conceptId` from `c2`
    (n = 109 unique concepts)
```
(iv) Concept Identifiers of all unique subtype concepts of AIDS-associated disorder concepts (above)

CREATE VIEW c4 AS
SELECT DISTINCT subtypeId
FROM transitiveclosure_20140131
JOIN c3 ON supertypeId=conceptId
(n = 110 unique concepts)

c201401 is the concepts table
d201401 is the description table
r201401 is the relationship table
Appendix 7.2: 
WHO clinical staging list used at the JOOTRH

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Stage 1</td>
</tr>
<tr>
<td>1. Asymptomatic</td>
</tr>
<tr>
<td>2. Persistent generalized lymphadenopathy</td>
</tr>
<tr>
<td>Clinical Stage 2</td>
</tr>
<tr>
<td>1. Moderate unexplained weight loss (&lt;10% of presumed or measured body weight)</td>
</tr>
<tr>
<td>2. Minor mucocutaneous manifestations (seborrheic dermatitis, papular pruritic eruptions, fungal nail infections, recurrent oral ulcerations, angular cheilitis)</td>
</tr>
<tr>
<td>3. Herpes zoster</td>
</tr>
<tr>
<td>4. Recurrent upper respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, abanygitis)</td>
</tr>
<tr>
<td>Clinical Stage 3</td>
</tr>
<tr>
<td>1. Unexplained severe weight loss (over 10% of presumed or measured body weight)</td>
</tr>
<tr>
<td>2. Unexplained chronic diarrhea for longer than one month</td>
</tr>
<tr>
<td>3. Unexplained persistent fever (intermittent or constant for longer than one month)</td>
</tr>
<tr>
<td>4. Persistent oral candidiasis</td>
</tr>
<tr>
<td>5. Oral hairy leukoplakia</td>
</tr>
<tr>
<td>6. Pulmonary tuberculosis</td>
</tr>
<tr>
<td>7. Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)</td>
</tr>
<tr>
<td>8. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis</td>
</tr>
<tr>
<td>9. Unexplained anemia (below 8g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopenia (below 50 x 10^9/l)</td>
</tr>
<tr>
<td>Clinical Stage 4</td>
</tr>
<tr>
<td>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations</td>
</tr>
<tr>
<td>1. HIV wasting syndrome</td>
</tr>
<tr>
<td>2. Pneumocystis jirovecii pneumonia (PCP)</td>
</tr>
<tr>
<td>3. Recurrent severe bacterial pneumonia (&gt;2 episodes within 1 year)</td>
</tr>
<tr>
<td>4. Cryptococcal meningitis</td>
</tr>
<tr>
<td>5. Toxoplasmosis of the brain</td>
</tr>
<tr>
<td>6. Chronic orolabial, genital or ano-rectal herpes simplex infection for &gt;1 month</td>
</tr>
<tr>
<td>7. Kaposi Sarcoma</td>
</tr>
<tr>
<td>8. HIV encephalopathy</td>
</tr>
<tr>
<td>9. Extrapulmonary tuberculosis</td>
</tr>
<tr>
<td>Conditions where confirmatory diagnosis testing is necessary:</td>
</tr>
<tr>
<td>1. Cryptosporidiosis, with diarrhea &gt;1 month</td>
</tr>
<tr>
<td>2. Hpsrosis</td>
</tr>
<tr>
<td>3. Cryptococcosis (extrapulmonary)</td>
</tr>
<tr>
<td>4. Disseminated non-tuberculous mycobacterial infection</td>
</tr>
<tr>
<td>5. Cytomegalovirus (CMV) retinitis or infection of the organs (other than liver, spleen, or lymph nodes)</td>
</tr>
<tr>
<td>6. Progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>7. Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis)</td>
</tr>
<tr>
<td>8. Candidiasis of the oesophagus or airways</td>
</tr>
<tr>
<td>9. Non-typhoid salmonella (NTS) septicaemia</td>
</tr>
<tr>
<td>10. Lymphoma cerebral or B cell Non Hodgkins’s Lymphoma</td>
</tr>
<tr>
<td>11. Invasive cervical cancer</td>
</tr>
<tr>
<td>12. Visceral leishmaniasis</td>
</tr>
<tr>
<td>13. Symptomatic HIV associated nephropathy or HIV associated cardiomyopathy</td>
</tr>
</tbody>
</table>
Chapter 8

General Discussion
8.1 Introduction

The main objective of this thesis was to gain new knowledge on the effectiveness of Electronic Medical Record (EMR) and Clinical Decision Support System (CDSS) on quality of HIV care and treatment in resource-constrained settings. In order to achieve this objective, we conducted several epidemiologic and informatics studies in Kenya around the specific research questions listed below:

(i) What are the socio-demographic, behavioral and biological risk factors associated with HIV infection among sexually active adults in Kenya?
(ii) Are EMRs associated with enhanced quality of HIV care and treatment in resource-limited settings?
(iii) What is the effect of CDSS on quality of HIV care and treatment in resource-limited settings?
(iv) Does SNOMED CT cover AIDS defining illnesses and can it be used to develop and implement an interface terminology in an EMR in a busy HIV clinic in sub-Saharan Africa in order to automatically derive WHO clinical staging of HIV?

The research questions were addressed in chapter 2 to chapter 7 of this thesis. In this final chapter, we present a synthesis and overview of the key findings of the studies included in the thesis. We discuss the strengths and weaknesses of our studies and compare the findings to published research conducted elsewhere. Implications of the study findings are also presented and we conclude by making some recommendations for further research.

8.2 Summary of key findings and comparison to related research

8.2.1 HIV epidemiology in Kenya

Research question (i) was addressed through an epidemiologic study based on the Kenya AIDS Indicator Survey (KAIS) 2007 and presented in chapter 2. The main objective of this study was to gain understanding of the correlates for HIV infection among sexually active adults in Kenya aged 15-64 years. The national HIV prevalence among sexually active adults aged 15-64 years was 7.4% while HIV prevalence in Nyanza province among a similar population was 16.9% - the highest infection rate in the country (1). The sub-analysis focusing on Nyanza province provided in-depth information on factors associated with HIV-infection among sexually active adults in this geographic region. The key correlates for HIV infection were Herpes Simplex Virus type 2 (HSV-II), multiple sexual partners, divorce/separation, consistent condom use with last sex partner among those who know their HIV-positive status, and lack of circumcision among men (1). In comparison to the Kenya Demographic Health Survey conducted in 2003 (KDHS 2003), there was a marginal increase in HIV prevalence but this was not statistically significant. The introduction of antiretroviral therapy (ART) which has been shown to reduce HIV-related mortality (2) may have contributed to the marginal increase in prevalence. Our study, however, did not report on HIV incidence. Condom use during sexual intercourse is known to reduce the risk of HIV transmission. HIV-infected persons who were aware of their HIV-positive status were four times more likely to use a condom (3;4).
Studies with similar findings used hospital-based data or targeted only one district in Nyanza province (5;6). The Kenya Demographic Health Survey (KDHS) which provided national and provincial level HIV prevalence estimates did not collect information on bio-behavioral indicators associated with HIV (7).

8.2.2 EMR use and compliance with HIV care and treatment guidelines

Research question (ii) was addressed in chapter 3 and chapter 4. In chapter 3, we showed that EMR use was associated with all three investigated outcome measures of quality for pre-ART care. EMR use was associated with a significantly higher rate of performing a baseline CD4+ T-cell count test compared to the paper system. Although the proportion of follow-up CD4+ T-cell count tests performed was low when using paper or EMR system, the rate was higher using EMR compared to the paper system. EMR use was associated with better compliance with the pre-ART guidelines which recommend performing a CD4+ T-cell count every six months. The study also showed that some follow-up CD4+ T-cell count tests were conducted earlier than 6 months – especially after the implementation of EMRs. Clinicians can order earlier CD4+ T-cell count if they suspect treatment failure or the previous test was conducted when the patient had an acute infection. EMR use also contributed to improved data quality. It was noted that data clerks add a layer of data quality checks during data entry into the EMRs and consult with clinicians whenever they encounter missing data.

Timely initiation of ART among eligible patients as recommended in the clinical guidelines improves treatment outcomes (8). In chapter 4, we showed that EMR use was associated with an increase in the likelihood of ART initiation among eligible patients receiving HIV care. Although there was a marginal reduction in time from ART eligibility to ART initiation after transitioning from paper system to EMR, this reduction was not clinically significant. Non-EMR factors such as clinician behavior (provider practice), time for patient preparation and the patient’s own readiness for ART could have contributed to the lack of time reduction to ART initiation (9;10). The proportion of ART-eligible patients receiving ART at the study sites (80%) was higher than The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2011 estimate for sub-Saharan Africa (56%) (11). However, there is still a 20% under-treatment, which requires other approaches for patient tracing and pre-ART counseling to ensure that all eligible patients are initiated on ART. We did not encounter any cases of over-treatment in our studies (i.e. initiating ART among ineligible patients) as the ART-eligibility criteria are well defined in the guidelines and understood by clinicians.

8.2.3 CDSS and quality of HIV care

Chapter 5 and chapter 6 address research question (iii). The findings from a systematic literature review to identify original, published studies describing the association between EMR-based CDSS and quality of HIV-care as well as barriers to EMR implementation in resource-limited settings are discussed in chapter 5. Twelve studies met the inclusion criteria set in the systematic review – ten of which were conducted in SSA and two others in the Caribbean. Only three studies quantified the associations between CDSS and relevant outcome and process measures, including time to order CD4+ T-cell tests, patient waiting time and missed appointments. One of the findings from the systematic review was that CDSS was associated with improved data quality. The majority of studies showed that data capture is by paper-
based systems which are retrospectively entered into an electronic system with CDSS. Only one study reported direct data entry at the point of care.

Immunological treatment failure among HIV patients occurs when there is sub-optimal response by the immune system to ART. With the increasing number of HIV patients receiving ART, CDSS can potentially help in detecting treatment failure and recommend appropriate clinical action. In chapter 6, we showed that the use of CDSS was associated with a higher likelihood of clinicians taking appropriate action on immunological treatment failure as recommended in the HIV treatment guidelines. There was a substantial reduction in time from immunological treatment failure to appropriate action following the use of CDSS. CDSS was also associated with faster ordering of baseline CD4+ T-cell test (a key measure of the state of a patient’s immune system) and timely ordering follow-up CD4+ T-cell test. The recording of CD4 T-cell tests in CDSS sites was significantly higher compared to EMR only sites. Previous studies on effect of EMR on quality of HIV care reported low rates of recording of CD4 T-cell counts, hence room for improvement through innovative approaches such as CDSS (12;13). Although CDSS was shown to be an effective intervention in enhancing guidelines adherence, it is worth noting that there is still large room for improving the recording of actions taken by clinicians. Nearly 45% of patients experiencing treatment failure did not have a recorded action and it is unclear whether no actions were taken or actions were taken but never recorded. A larger proportion of patients in the intervention group compared to the control group had a recording of condition for treatment failure and the action taken (54.9% vs. 29.5%). Lack of data could potentially affect the continuity of HIV care, especially in cases where a patient is seen by different clinicians. The choice of decision rules in the CDSS was limited to the use of CD4+ T-cell to infer eligibility for ART and monitor immunological response to HIV treatment. However, other clinical decisions, including ART eligibility, are based on diagnoses and these require structured coded data for accurate inference.

The findings from our studies that relate to CDSS and quality of care were largely consistent with research done in developed countries (14-16). Studies by Williams, Were and Alamo – all conducted in resource-limited settings – showed that CDSS can enhance quality of HIV care through better adherence to guidelines and improved processes (e.g. reduced patient waiting time and timely ordering of laboratory tests) (17-19). The strength of associations demonstrated in the studies published in this thesis, especially the use of CDSS in HIV care (chapter 6), makes them stand out. Poor data quality was reported as a key hindrance to meaningful use of CDSS (19-21).

Barriers to CDSS implementation in resource-limited settings included weak infrastructure and human resource challenges e.g. unreliable electric power, poor Internet connectivity, inadequate computers, poorly trained health workers and low computer literacy (22;23). These challenges are unique to resource-limited settings, especially in SSA and are quite different from those experienced in developed countries e.g. inability to type quickly, reduced eye contact between clinician and patient during consultation and preference to write in long prose (24;25). Implementation of CDSSs and evaluation studies in resource-limited settings are generally premature as shown by the basic design of the studies included in the review. This is despite substantial investments by global health initiatives in health systems strengthening in SSA. It is important to note that the use of EMRs and CDSS is rising mainly due to these global health initiatives.
8.2.4 Structured recording of AIDS defining illnesses

To address research question (iv), a structured approach to deriving a reference set for AIDS Defining Illnesses (ADIs) based on an earlier published framework for developing interface terminologies (26) is described in chapter 7. The aim of this study was to improve data quality through standardized recording of ADIs using a terminology system (SNOMED CT) which has been shown to enhance data accuracy, completeness and reusability in developed countries (27;28). More than 1,000 concepts described by nearly 1,900 terms were derived from four different sources. SNOMED CT had a near-complete content-coverage of the pre-coordinated concepts currently used in clinical HIV practice of a Kenyan teaching and referral hospital. The resulting reference set was implemented as an interface terminology of OpenMRS EMR to standardize the recording of ADIs, and for automated inference of WHO clinical stage to determine ART eligibility based on HIV disease progression. Based on experiences elsewhere, it is expected that the use of a reference set will enhance the quality of data recorded leading to more accurate inference of WHO staging and appropriate decisions on clinical care (28). These solutions, however, do not entirely address the problem of missing data. Further qualitative studies are needed to understand reasons why clinicians do not record data and how these can be comprehensively addressed.

8.3 Strengths and weaknesses of the studies

The Kenya AIDS Indicator Survey (KAIS), which was a nationally representative, population-based survey with response rate above 70%, provided key epidemiologic data that helped inform the location of our evaluation studies (chapter 2). KAIS was powered to provide provincial level estimates and the survey showed that Nyanza province had the highest rate of HIV infection in Kenya. Our studies evaluating the effect of EMR and CDSS on quality of care were conducted in Siaya and Kisumu counties, both located in Nyanza province.

The studies were conducted in multiple clinics and had large sample sizes which improved the precision of estimates. The study on standardization of AIDS-defining illnesses benefited from data collection from a busy teaching and referral hospital that provides HIV care and treatment to a large number of patients with diverse conditions hence a broad coverage of terms used to describe ADIs. Another positive aspect of the studies described in this thesis is that all HIV clinics in Kenya use the same national HIV care and treatment guidelines adapted from the WHO guidelines. The Kenyan Ministry of Health (MOH) HIV treatment guidelines were revised just before the start of the study, raising the threshold for ART eligibility from 250 cells/µl to 350 cells/µl. This had the benefit of increasing the number of patients enrolled initiating ART and had a similar effect on the intervention and control sites. All EMRs with CDSS need to comply with a single set of national guidelines which are revised periodically. The launch of the new HIV treatment guidelines by WHO in June 2013 shifts focus on routine HIV treatment monitoring from CD4+ T-cell count to viral load. Kenya is currently in the process of transitioning from immunological to virological monitoring of patients receiving ART. The effect of the new guidelines was minimal on our studies since the Kenyan MOH guidelines were not revised until June 2014, more than six months after the completion of our data collection. Moreover, we believe that the strong effects demonstrated in our study are likely to be generalizable towards improved virological monitoring of
patients receiving ART as recommended in the new guidelines. The decision rule for detecting virological treatment failure is similar to that of detecting immunological treatment failure.

We did not have to replace any existing system in order to implement our studies. Although a number of EMRs are implemented in Kenya, all our studies focused on two systems, namely C-PAD for the studies in Siaya county (chapters 3, 4 and 6) and OpenMRS for the studies at the teaching and referral hospital in Kisumu county (chapter 7). The team, therefore, did not have to deal with stringent administrative bureaucracy, user training and change management involved in replacing systems.

Our studies had some weaknesses. A weakness of the KAIS is that the sexual-behavioral data reported were based on self-reporting by survey respondents. Due to sensitivities around sexual behavior, some of this information may be inaccurate. However, the interviewers were well trained on ensuring respondents’ confidentiality and on eliciting the most accurate responses, even to the most sensitive topics. The survey design was cross-sectional and may not show causality.

The design for two of our studies described in chapter 3 and chapter 4 was a “retrospective observational, before-and-after” and we were not able to determine a cause-effect relation between the use of EMR and the outcome variables. Similar limitations were reported in most evaluation studies conducted in SSA. In addition to the two studies, we conducted a prospective, cluster randomized controlled study to understand the association between EMR-based CDSS and detection and action on immunological treatment failure. The limitations of determining the cause-effect were addressed through the prospective, randomized design. Health workers’ low computer literacy and frequent transfer of clinicians and nurses trained on the systems were major impediments to the implementation and use of EMRs at the study sites. As the studies were conducted in MOH-owned clinics, policies around staffing were the prerogative of the MOH and beyond the control of the study team. In order to mitigate the effects of staff transfers, the clinicians and nurses were constantly trained to ensure that they were able to use the systems correctly in accordance with the study protocol. Poor data quality, especially in the retrospective studies described in chapter 3 and chapter 4, was a major problem. Missing data on key variables such as CD4+ T-cell test dates and results, enrolment date and ART eligibility date reduced the number of records that were included in our final analyses. A number of sites were excluded from our randomized controlled trial since they did not have reliable electric power or secure location to place the computers.

8.4 Relevance and implications of the study findings

Advances in the use of health IT, especially EMR-based CDSS in developed countries, have significantly contributed to improved quality of healthcare. This has been achieved through better compliance with guidelines, better diagnosis and reduced medication errors (29-31). SSA has particularly lagged behind in the adoption and use of health IT due to numerous challenges outlined in studies by Forster and Fraser (22;23). With the evidence from our studies which show that EMR and CDSS use can improve data quality and adherence to treatment guidelines, there is a compelling reason for further investments in addition to those by current initiatives such as the US President’s Emergency Plan for AIDS Relief.
(PEPFAR) and the Global Fund Against AIDS, TB and Malaria (GFATM) to strengthen health information systems in order to enhance continuity of high quality health care.

The studies included in this thesis were conducted through a partnership between the US Centers for Disease Control and Prevention (CDC) and the MOH through the Kenya Medical Research Institute (KEMRI) to generate evidence on the role of EMRs and CDSS in enhancing quality of HIV care. These evaluations are part of an ambitious project to implement EMRs at 600 health facilities nationally. As EMRs and CDSS were only introduced at the study clinics over the last 2-5 years, the findings from these studies will promote their use and justify further investments in EMRs in Kenya by the MOH and its partners. All stakeholders agreed that existing EMRs, none of which had a functional CDSS, would be upgraded at the end of the studies in case of positive results. The design of our studies, including a randomized controlled trial, was robust and we expect that the findings can be generalized to health facilities in resource-limited settings in SSA. The majority of HIV patients seek treatment at MOH-owned clinics, which also happen to be under-resourced compared to private hospitals.

Late initiation of ART among eligible patients results in poor outcomes including higher mortality (32). We showed that EMRs can improve the likelihood of ART-eligible patients getting initiated on ART hence better outcomes. Wide-scale use of EMRs will imply that more ART-eligible patients currently not receiving ART will be initiated on therapy. Additionally, timely performance of the routine laboratory tests for HIV treatment monitoring enables clinicians to make timely decisions on patient management. Patients who experience treatment failure are likely to be identified earlier and appropriate action taken according to treatment guidelines.

WHO’s 2013 consolidated guidelines for HIV prevention and treatment recommend the use of viral load monitoring of HIV treatment (33). As countries in SSA, including Kenya, continue to scale-up the use of viral load to monitor response to HIV treatment nationally, there is a critical need to use automated systems to inform clinicians of treatment outcomes such as viral suppression, loss to follow-up or death (33). We expect that our experience with the use of CDSS to identify patients who were experiencing immunological treatment failure can be readily applied to the new guidelines to identify patients experiencing virological treatment failure. Automated alerts to clinicians will enable them take appropriate clinical action.

Use of terminology systems such as SNOMED CT to support documentation has been shown to enhance data completeness and reusability which improves continuity of care (27;28). Automated inference of WHO clinical stage through accurate recording of diagnosis based on a terminology system ensures that patients are correctly classified based on HIV disease progression hence appropriate initiation of ART. The ADI reference set derived from one of our studies is being used to implement an interface terminology which will improve the documentation of ADIs at a busy referral hospital. With more complete reporting, we will be addressing the problem of under-reporting of ADI which is common in SSA countries as reported by Kiragga et al. (21). The introduction of a terminology system to support documentation of patient records was welcomed by the stakeholders and will be extended to other areas including the tuberculosis (TB) and maternal and child health (MCH) clinics to improve data reuse and automated generation of summary statistics. CDSSs will be implemented using standardized
recording of ADIs to support automated inference of WHO clinical stage and to alert clinicians on patient eligibility for ART initiation.

Our studies identified opportunities and challenges in implementing health IT in resource limited settings including infrastructural and human capacity. The inability to implement EMRs and CDSSs in real-time as a point of care system due to lack of reliable electric power at many of the clinics was a major challenge. The Government should invest in innovative methods of generating electric power such as those based on solar or wind energy to ensure reliable electricity. This was also recommended by Fraser et al. (34). Government of Kenya initiatives such as the ongoing rural electrification program (REP) which aims at providing reliable electricity to hospitals and schools in rural areas will in the near future solve the electric power problem in many health facilities. We showed gaps in information on the benefits or problems of implementing EMR-based CDSSs due to inadequate research done in resource limited setting. Well-designed and rigorous evaluations will generate relevant evidence to inform investments in technologies that work in settings with unique challenges (e.g. SSA) in the way that studies conducted in developed countries and described in systematic reviews have informed the implementation of CDSS in those countries (14-16). Our study on early detection and action of immunological treatment failure among patients receiving ART (chapter 6) is a first example of such a rigorous evaluation study.

8.5 Recommendations for further research

There have been substantial investments in strengthening health IT in resource-limited settings, including SSA, over the last 5 years. However, there is inadequate evidence to show what technologies work and the barriers to the implementation of such technologies. There is need for more rigorous evaluations studies, including randomized controlled trials to assess associations between EMR-based CDSS and processes and outcomes for HIV care and other chronic illnesses (Figure 8.1). Such studies should take into account overall improvement in the health systems including additional laboratory capacity, increased computer literacy levels of health workers and improved Internet coverage - especially in rural areas.

Provider practice plays a critical role in provision of HIV care. Garg et al. showed that CDSSs can improve practitioner practice in developed countries (14). No such studies have been conducted in resource-limited settings. There is need for qualitative studies on clinicians’ perspectives in relation to usability of EMRs and CDSSs and barriers to their successful implementation. Noormohammad et al. described reasons why clinicians do not comply with CDSS recommendations in a study conducted in Kenya, but did not discuss issues around usability of the EMR or CDSS (35). Such studies would supplement the existing work which are largely based on quantitative methods.
Very few studies have been conducted to evaluate the effectiveness of terminology systems on data quality and quality of care. Although Shah et al. reported that use of a structured clinical terminology system contributed to improved data accuracy at clinics in the United Kingdom, similar studies are yet to be conducted in resource-limited settings as well as developed settings (28). We described the implementation of an interface terminology based on SNOMED CT but did not evaluate its effect on data quality and quality of HIV care indicators such as accurate clinical staging of patients and appropriate initiation on ART. This is recommended for a future study.

Prior to conducting the evaluation studies, more work needs to be done to improve the ICT infrastructure (including Internet connectivity) and human capacity on health IT in resource-limited settings as recommended in various chapters of this thesis and in studies by Forster and Fraser et al (22;34). The Kenya eHealth Strategy that was launched in 2011 highlights the strengthening of ICT infrastructure as a priority area (36). The Government of Kenya, together with private sector players, has continued to extend Internet connectivity to all districts, including remote locations that were previously not served. County governments are also providing computers to health facilities and ensuring adequate physical security of the computer equipment as a way of enhancing the use of computer systems to improve quality of healthcare. Policies on health IT capacity building for health workers, hinged on the eHealth strategy, should be promoted to ensure that there are adequate skills to meaningfully use EMRs and CDSSs to provide clinical care. We recommend an overall training program for health workers on the importance of recording high quality data alongside specific training on the optimal use of the EMRs they will work with. Initiatives which promote regular use of data at the point of generation may also help reduce the proportion of missing data. Formal training on medical informatics at post-graduate level in local universities is taking root while the use of eLearning platforms to train healthcare workers on various courses including IT and monitoring and evaluation are becoming increasingly common.
8.6 Conclusion

Our studies showed that Nyanza province has the highest HIV prevalence in Kenya. We evaluated EMR and CDSS use at health facilities in Nyanza province and found that EMRs were associated with enhanced quality of HIV care through better adherence to HIV treatment guidelines. We showed that a CDSS causes early action on immunological treatment failure among patients receiving ART in a resource limited setting. Finally, we found that different sources demonstrate complementarity in the derivation of concepts and terms for an interface terminology that is based on SNOMED CT in order to automatically derive WHO clinical staging of HIV.
Reference List


Summary
Sub-Saharan Africa (SSA) bears a disproportionately high burden of the HIV epidemic despite global efforts to combat the virus that causes AIDS. The WHO and The Joint United Nations Programme on HIV/AIDS (UNAIDS) joint report on global HIV epidemic showed that nearly two-thirds of the 34 million people infected with the virus resided in SSA in 2010 and morbidity and mortality remain high. In order to plan for effective interventions to respond to the HIV epidemic, it is necessary to understand the socio-demographic, behavioral and biological factors associated with the disease. Various sources of data including routine statistical summaries, surveys, surveillance, operational research and mathematical modeling are used to monitor the distribution and trends in the epidemic and to plan prevention and treatment programs.

WHO develops and routinely reviews guidelines for HIV prevention, care and treatment. Many countries, including Kenya, have adopted these guidelines and customized them to be most appropriate in addressing the local epidemic. WHO released key guidelines in 2006 and 2010. Guidelines released in 2010 recommended the use of CD4 T-cell count to assess eligibility for antiretroviral therapy (ART) and to monitor the patient’s immune system’s response to ART. CD4 T-cells are white cells that are an essential part of the body’s immune system. Various studies have shown that CD4 T-cell count and viral load are the key prognostic factors for HIV disease progression to AIDS and death. Early mortality is higher among patients enrolling on HIV care with low baseline CD4 T-cell count. The HIV treatment guidelines recommend conducting CD4 T-cell measurements during enrollment in HIV care (baseline) and follow-up tests every 6 months to monitor response to treatment. Immunological treatment failure occurs when there is sub-optimal response by the immune system to ART. The guidelines also recommend the use of clinical presentation of patients to classify the progression of HIV infection by classifying common co-morbidities known to be associated with HIV into four clinical stages based on the severity and prognosis. The clinical conditions range from asymptomatic to conditions where presumptive diagnoses can be made on the basis of clinical presentation or simple investigations.

Enforcing adherence to guidelines can be challenging in resource-limited settings such as SSA where inadequate health workers (including nurses and clinicians) serve a disproportionately large number of patients. Patients newly enrolled on ART should visit the clinic monthly, while stable patients are expected to attend the clinic every three months for review and medication refills. AIDS, like other chronic diseases, requires lifelong treatment and ongoing collection of longitudinal data to monitor the response to treatment at individual patient level and for routine statistical reporting. The rapidly increasing number of patients enrolling on HIV treatment in SSA annually, coupled with a limited number of health workers, can potentially compromise the recording of patient data and hence quality of care. In order to address this, there is urgent need for innovative solutions such as Electronic Medical Records (EMRs) for the management of the large amounts of longitudinal data, and Clinical Decision Support Systems (CDSS) for providing feedback to health care workers to improve guideline adherence. Studies in developed countries have shown that EMRs and CDSSs are associated with better diagnosis, reduced medication errors, improved data quality and better practitioner performance.

SSA has lagged behind in the adoption of EMRs and CDSS and continues to use paper-based recording of patient data. Obstacles to implementation of EMRs include unique challenges such as unreliable or unavailable electric power, inadequate computers and poor or no access to the Internet, coupled with
health workers’ limited computer skills, especially in rural areas where the majority of the patients seek treatment. Unstructured collection and free-text recording of key data elements such as diagnoses limits data quality and data re-usability for decision support or statistical analysis.

The majority of published studies so far that have used rigorous scientific methods to evaluate associations between health IT interventions, such as EMRs and CDSSs, and selected quality of care outcomes were conducted in developed countries. Countries in SSA, which also have the weakest health systems, have not conducted adequate, well designed studies to understand the effect of EMRs and CDSS on quality of care for major diseases such as HIV/AIDS. With the increasing investment in health systems including EMRs and other systems in SSA, there is a critical need to evaluate the effect of such systems on quality of care. These evaluations would inform appropriate investments in solutions that address context-specific problems while taking into account unique challenges of implementing health IT interventions in resource-limited settings.

The research work published in this thesis describes HIV epidemiology in Kenya, a systematic review on EMR-based CDSS in resource-limited settings and associations and effects between EMR/CDSS and quality of care in Kenya.

Understanding HIV epidemiology is essential in appropriate planning for the national response and monitoring of the disease at population and individual patient levels. In chapter 2, we described an epidemiologic study, based on the Kenya AIDS Indicator Survey (KAIS) conducted in 2007. Our study provided a broad overview of the distribution of the HIV epidemic and correlates for HIV infection among sexually active adults aged 15-64 years residing in Kenya. The national HIV prevalence among sexually active adults aged 15-64 years was 7.4% while HIV prevalence in Nyanza province among a similar population was 16.9% - the highest infection rate in the country. The key correlates for HIV infection were Herpes Simplex Virus type 2 (HSV-II), multiple sexual partners, divorce/separation, consistent condom use with last sex partner among those who know their HIV-positive status, and lack of circumcision among men. Condom use during sexual intercourse is known to reduce the risk of HIV transmission. HIV-infected persons who were aware of their HIV-positive status were four times more likely to use a condom. In comparison to the Kenya Demographic Health Survey conducted in 2003, there was a marginal increase in HIV prevalence but this was not statistically significant. The introduction of antiretroviral therapy (ART) which has been shown to reduce HIV-related mortality may have contributed to the marginal increase in prevalence. Our study, however, did not report on HIV incidence.

Pre-ART care is essential for HIV-positive patients who have not become eligible to ART based on the WHO guidelines. Chapter 3 describes the findings of a “before-after” study on adherence to pre-ART guidelines following the introduction of an EMR in 17 clinics in Nyanza province, western Kenya. We showed that EMR use was associated with all three investigated outcome measures of quality for pre-ART care. EMR use was associated with a significantly higher rate of performing a baseline CD4+ T-cell count test compared to the paper system. Although the proportion of follow-up CD4+ T-cell count tests performed was low when using paper or EMR system, the rate was higher using EMR compared to the paper system. EMR use was associated with a reduction in the time from enrolment of HIV care to the
conducting baseline CD4+ T-cell test. EMR use was associated with better compliance with the pre-ART guidelines which recommend performing a CD4+ T-cell count every six months (timeliness of performing CD4+ T-cell tests). EMR use also contributed to improved data quality. It was noted that data clerks, who enter patient data into the EMR, add a layer of data quality checks during data entry and consult with clinicians whenever they encounter missing data.

In chapter 4, we present the results of a multi-center “before-after” study evaluating the association between EMR and appropriate placement/initiation of HIV-infected patients on ART. The study was conducted in the same 17 health facilities described in chapter 3. We showed that EMR use was associated with an increase in the likelihood of ART initiation among eligible patients receiving HIV care. Although there was a marginal reduction in time from ART eligibility to ART initiation after transitioning from paper system to EMR, this reduction was not clinically significant. Non-EMR factors such as clinician behavior (provider practice), time for patient preparation and the patient’s own readiness for ART could have contributed to the lack of time reduction to ART initiation. The proportion of ART-eligible patients receiving ART at the study sites (80%) was higher than The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2011 estimate for SSA (56%). However, there is still a 20% under-treatment, which requires other approaches for patient tracing and pre-ART counseling to ensure that all eligible patients are initiated on ART. We did not encounter any cases of over-treatment in our studies (i.e. initiating ART among ineligible patients) as the ART-eligibility criteria are well defined in the guidelines and understood by clinicians.

In order to learn from the evaluation studies on the effects of EMR-based CDSS on quality of HIV care, we conducted a systematic review to identify original, published studies describing the association between EMR-based CDSS and quality of HIV-care as well as barriers to EMR implementation in resource-limited settings, including SSA. The findings from a systematic review are discussed in chapter 5. Twelve studies met the inclusion criteria set in the systematic review – ten of which were conducted in SSA and two others in the Caribbean. Only three studies quantified the associations between CDSS and relevant outcome and process measures, including time to order CD4+ T-cell tests, patient waiting time and missed appointments. One of the findings from the systematic review was that CDSS was associated with improved data quality. The majority of studies showed that data capture is by paper-based systems which are retrospectively entered into an electronic system with CDSS. Only one study reported direct data entry at the point of care. Implementation of CDSSs and evaluation studies in resource-limited settings are generally premature as shown by the basic design of the studies included in the review. This is despite substantial investments by global health initiatives in health systems strengthening in SSA. It is important to note that the use of EMRs and CDSS is rising mainly due to these global health initiatives.

Immunological treatment failure among HIV patients occurs when there is sub-optimal response by the immune system to ART. With the increasing number of HIV patients receiving ART, CDSS can potentially help in detecting treatment failure and recommend appropriate clinical action. Chapter 6 describes the findings of a multi-center cluster randomized controlled trial to assess the effect of EMR-based CDSS on early detection of immunological treatment failure among HIV-infected patients at 13 clinics in Nyanza province, western Kenya. The study presents the implementation of a CDSS to detect immunological
treatment failure in compliance with the treatment guidelines and recommending appropriate clinical action. We showed that the use of CDSS was associated with a higher likelihood of clinicians taking appropriate action on immunological treatment failure as recommended in the HIV treatment guidelines. There was a substantial reduction in time from immunological treatment failure to appropriate action following the use of CDSS. CDSS was also associated with faster ordering of baseline CD4+ T-cell test (a key measure of the state of a patient’s immune system) and timely ordering follow-up CD4+ T-cell test. The recording of CD4 T-cell tests in CDSS sites was significantly higher compared to EMR only sites. Previous studies on effect of EMR on quality of HIV care reported low rates of recording of CD4 T-cell counts, hence room for improvement through innovative approaches such as CDSS. Although CDSS was shown to be an effective intervention in enhancing guidelines adherence, it is worth noting that there is still large room for improving the recording of actions taken by clinicians. Nearly 45% of patients experiencing treatment failure did not have a recorded action. A larger proportion of patients in the intervention group compared to the control group had a recording of condition for treatment failure and the action taken (54.9% vs. 29.5%). Lack of data could potentially affect the continuity of HIV care, especially in cases where a patient is seen by different clinicians. The choice of decision rules in the CDSS was limited to the use of CD4+ T-cell to infer eligibility for ART and monitor immunological response to HIV treatment. However, other clinical decisions, including ART eligibility, are based on diagnoses and these require structured coded data for accurate inference.

Barriers to CDSS implementation in resource-limited settings included weak infrastructure and human resource challenges e.g. unreliable electric power, poor Internet connectivity, inadequate computers, poorly trained health workers and low computer literacy. These challenges are unique to resource-limited settings, especially in SSA and are quite different from those experienced in developed countries e.g. inability to type quickly, reduced eye contact between clinician and patient during consultation and preference to write in long prose.

Chapter 7 describes a structured approach to derive a comprehensive set of ADI concepts based on SNOMED CT and evaluates SNOMED CT’s content coverage for ADIs in a provincial referral hospital in Kenya. The aim of this study was to improve data quality through standardized recording of ADIs using a terminology system (SNOMED CT) which has been shown to enhance data accuracy, completeness and reusability in developed countries. More than 1,000 concepts described by nearly 1,900 terms were derived from four different sources. SNOMED CT had a near-complete content-coverage of the pre-coordinated concepts currently used in clinical HIV practice of a Kenyan teaching and referral hospital. The resulting reference set was implemented as an interface terminology of OpenMRS EMR to standardize the recording of ADIs, and for automated inference of WHO clinical stage to determine ART eligibility based on HIV disease progression. Based on studies conducted in other countries, it is expected that the use of a reference set will enhance the quality of data recorded leading to more accurate inference of WHO staging and appropriate decisions on clinical care.

We showed that EMRs can improve the likelihood of ART-eligible patients getting initiated on ART hence better outcomes. Wide-scale use of EMRs will imply that more ART-eligible patients currently not receiving ART will be initiated on therapy. Additionally, timely performance of the routine laboratory tests for HIV treatment monitoring enables clinicians to make timely decisions on patient management.
Patients who experience treatment failure are likely to be identified earlier and appropriate action taken according to treatment guidelines.

SSA has particularly lagged behind in the adoption and use of health IT due to numerous challenges outlined in studies included in this thesis and other studies conducted in resource-limited settings. With the evidence from our studies which show that EMR and CDSS use can improve adherence to treatment guidelines and data quality hence better quality of HIV care, there is a compelling reason for further investments in addition to those by current initiatives such as the US President’s Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund Against AIDS, TB and Malaria (GFATM) to strengthen health information systems in order to enhance continuity of high quality health care. The studies included in this thesis were conducted through a partnership between the US Centers for Disease Control and Prevention (CDC) and the Kenyan Ministry of Health through the Kenya Medical Research Institute (KEMRI) to generate evidence on the role of EMRs and CDSS in enhancing quality of HIV care. These evaluations are part of an ambitious project to implement EMRs at 600 health facilities nationally.

Our studies identified opportunities and challenges in implementing health IT in resource limited setting including infrastructural and human capacity. The inability to implement EMRs and CDSSs in real-time as a point of care system due to lack of reliable electric power at many of the clinics was a major challenge. The Government should invest in innovative methods of generating electric power such as those based on solar or wind energy to ensure reliable electricity. Government of Kenya initiatives such as the ongoing rural electrification program (REP) which aims at providing reliable electricity to hospitals and schools in rural areas will in the near future solve the electric power problem in many health facilities.

We showed gaps in information on the benefits or problems of implementing EMR-based CDSSs due to inadequate research done in resource limited setting. Well-designed and rigorous evaluations will generate relevant evidence to inform investments in technologies that work in settings with unique challenges (e.g. SSA) in the way that studies conducted in developed countries and described in systematic reviews have informed the implementation of CDSS in those countries. Our study on early detection and action of immunological treatment failure among patients receiving ART (chapter 6) is a first example of such a rigorous evaluation study.

There is need for more rigorous evaluations studies, including randomized controlled trials to assess associations between EMR-based CDSS and processes and outcomes for HIV care and other chronic illnesses. Prior to conducting such studies, more work needs to be done to improve the ICT infrastructure (including Internet connectivity) and human capacity on health IT in resource-limited settings. The evaluations studies should also take into account overall improvement in the health systems including additional laboratory capacity.
Samenvatting
Een onevenredig deel van de wereldwijde hiv-epidemie treft Sub-Sahara Afrika (SSA), ondanks wereldwijde inspanningen om het virus, dat aids veroorzaakt, te verslaan.

De WHO en de hiv/aids-programma’s van de Verenigde Naties (UNAIDS) rapporteren gezamenlijk dat in 2010 de wereldwijde hiv-epidemie 34 miljoen geïnfecteerde personen treft, waarvan tweederde woonachtig is in SSA, en dat de morbiditeit en mortaliteit hoog blijven. Om effectieve interventies voor de hiv-epidemie te ontwikkelen is kennis over sociodemografische, gedrags- en biologische factoren, welke geassocieerd zijn met de ziekte, noodzakelijk. Verschillende databronnen zoals routinematig verzamelde statistieken, vragenlijsten, surveillance, operationeel onderzoek en mathematische modellen worden gebruikt om de distributie van en de trends in de epidemie te monitoren en om behandel- en preventieplannen op te stellen.

De WHO ontwikkelt en updatet op regelmatige basis richtlijnen voor hiv-preventie, zorg en behandeling. Veel landen, waaronder Kenia, hebben deze richtlijnen geadopteerd en aan lokale omstandigheden aangepast zodat ze geschikt zijn om de lokale epidemic aan te pakken. De WHO heeft in 2006 en 2010 kernrichtlijnen uitgegeven. De richtlijnen uit 2010 bevelen aan om het aantal CD4+ T-cellen te gebruiken om te beoordelen of een patiënt moet starten met antiretrovirale therapie (ART) en om de reactie van het immuunsysteem van de patiënt op de ART te monitoren. CD4+ T-cellen zijn witte bloedcellen die een essentieel onderdeel vormen van het menselijk immuunsysteem. Verschillende studies hebben aangetoond dat het aantal CD4+ T-cellen en de viral load (‘virale last’) sterke prognostische factoren zijn voor de progressie van de ziekte van hiv naar aids. Patiënten die de hiv-zorg starten met een laag aantal CD4+ T-cellen hebben een hogere vroege mortaliteit dan patiënten met een hoog aantal CD4+ T-cellen.

De hiv-behandelrichtlijnen bevelen aan om het aantal CD4+ T-cellen te meten bij de start van de behandeling en vervolgens iedere 6 maanden om de reactie op de behandeling te monitoren. Immunologisch falen ontstaat wanneer het immuunsysteem suboptimaal reageert op de ART. De richtlijnen bevelen ook aan om de klinische presentatie van de patiënt te gebruiken om de progressie van de hiv-infectie te klasreer. Veevoorkomende co-morbiditeiten, waarvan bekend is dat ze geassocieerd zijn met hiv, worden gebruikt om vier klinische stadia van de ziekte op basis van ernst en prognose te definiëren. De klinische stadia variëren van asymptomatisch tot conditions waar voorlopige diagnoses kunnen worden gesteld op basis van klinische presentatie of eenvoudige lichamelijk en laboratoriumonderzoek.

Het bevorderen van de adherentie aan de richtlijnen is een uitdaging in ontwikkelingslanden zoals in SSA door het tekort aan juist gekwalificeerd zorgpersoneel (artsen, verpleegkundigen, laboratoriumpersoneel) en het onevenredig grote aantal patiënten. Patiënten die starten met ART moeten maandelijks de kliniek bezoeken, terwijl stabiele patiënten die nog niet gestart zijn met ART ook iedere drie maanden bij de kliniek verwacht worden voor controle en medicatie.

Aids vereist, net als andere chronische ziekten, een levenslange behandeling en een continue longitudinal verzameling van gegevens om de reactie van de patiënt op de behandeling te monitoren. Deze gegevens worden ook gebruikt voor reguliere statistische rapportage.
Het snel toenemend aantal patiënten dat een hiv-behandeling ondergaat, samen met het beperkte aantal zorgverleners, hebben een potentiële negatieve effect op de kwaliteit van de vastlegging van patiëntgegevens en daardoor op de kwaliteit van de zorg. Om hier het hoofd aan te bieden zijn innovatieve oplossingen noodzakelijk, zoals Elektronische PatiëntenDossiers (EPDs) voor het beheer van grote hoeveelheden patiëntgegevens, en klinische BeslissingsOndersteunende Systemen (BOSeN) om aan zorgverleners feedback te geven over hun handelen. Studies in voornamelijk Westerse landen hebben aangetoond dat EPDs en BOSeN geassocieerd zijn met betere diagnosen, minder medicatiefouten, verbeterde datakwaliteit en betere zorgprestaties door zorgverleners.

SSA loopt achter met het invoeren van EPDs en BOSeN en gebruikt vooral papieren dossiers voor het vastleggen van patiëntgegevens. Barrières voor de implementatie van EPDs omvatten onvoldoende en ontoereikende computers, slechte of geen toegang tot het internet, samen met gebrek aan de juiste computervaardigheden van het personeel, met name in afgelegen gebieden waar juist het aantal patiënten groot is. Ongestructureerde en vrije-teks opslag van belangrijke gegevenselementen zoals diagnosen heeft een negatieve invloed op de datakwaliteit en de mogelijkheden om deze gegevens te gebruiken in BOSeN en in statistische rapportages.

Verreweg de meeste studies naar de associatie tussen zorg-ict-interventies zoals EPDs of BOSeN en kwaliteit van zorg zijn uitgevoerd in de Westerse wereld. In de SSA landen, die gebukt gaan onder zwakke zorgsystemen, zijn geen adequate, goed opgezette studies uitgevoerd om het effect van EPDs en BOSeN op de kwaliteit van zorg van belangrijke ziekten zoals hiv/aids te onderzoeken. Doordat in SSA momenteel steeds meer investeringen in EPDs en andere informatiesystemen plaatsvinden, is het belangrijk het effect hiervan op de kwaliteit van zorg te evalueren. Deze evaluaties zouden moeten worden gebruikt om beslissingen over investeringen in zorg-ict te nemen, daarbij rekening houdend met de specifieke omstandigheden en uitdagingen voor het implementeren van zorg-ict binnen deze setting.

Het onderzoek dat in dit proefschrift is beschreven omvat een beschrijving van de hiv-epidemiologie in Kenia, een systematische literatuur-review naar EPDs met een BOS-functionaliteit in ontwikkelingslanden en studies naar associaties en effecten van EPD- en BOS-implementaties op de kwaliteit van zorg in Kenia.

Inzicht in de hiv-epidemiologie is belangrijk om nationale programma’s voor het behandelen en monitornen van de ziekte op populatie- en patiëntniveau op de juiste manier te plannen. In hoofdstuk 2 beschrijven we een epidemiologische studie gebaseerd op de Keniaanse Aids Indicator Survey (KAIS) uitgevoerd in 2007. Onze studie geeft een algemene overzicht van de verspreiding van de hiv-epidemie onder seksueel actieve volwassenen van 15 tot 64 jaar die woonachtig zijn in Kenia. De landelijke hiv-prevalentie onder seksueel actieve volwassenen van 15 tot 64 jaar was 7,4%, terwijl de hiv-prevalentie in de provincie Nyanza, in het westen van Kenia, onder dezelfde populatie 16,9% was, het hoogste infectiepercentage in het land. De belangrijkste determinanten voor hiv-infectie waren Herpes Simplex Virus type 2 (HSV-II), meerdere sekspartners, echtscheiding/separatie, consequent condoomgebruik met de laatste sekspartner onder hen die weten dat ze hiv-positief zijn, en de afwezigheid van circumcisie onder mannen. Het is bekend dat condoomgebruik tijdens seksueel verkeer het risico op het overdragen
van hiv reduceert. Mensen die weten dat ze hiv-positief zijn gebruikten vier keer zo vaak een condoom. In vergelijking met de Kenya Demographic Health Survey uitgevoerd in 2003, was er een marginale toename van de hiv-prevalentie maar deze was niet statistisch significant. De introductie van ART, waarvoor is aangetoond dat het de hiv-gerelateerde mortaliteit reduceert, kan bijgedragen hebben aan deze slechts marginale toename in de prevalentie. Onze studie bevat helaas geen informatie over de hiv-incidentie.

Volgens de WHO-richtlijnen is pre-ART zorg essentieel voor hiv-positieve patiënten die nog niet voor ART in aanmerking komen. **Hoofdstuk 3** beschrijft een studie naar de adherentie aan de pre-ART-richtlijnen voor en na de introductie van een EPD in 17 klinieken in de provincie Nyanza. We lieten zien dat EPD-gebruik geassocieerd was met alle drie de onderzochte uitkomsten voor kwaliteit van pre-ART-zorg. EPD-gebruik was geassocieerd met een significant hoger percentage uitgevoerde metingen van het aantal CD4⁺ T-cellen bij aanvang van de zorg (baseline) vergeleken met de situatie waarin papieren dossiers werden gebruikt. Hoewel het percentage vervolgemetingen van het aantal CD4⁺ T-cellen laag was in zowel de situatie met een EPD als die met een papieren dossier, was het percentage in de EPD-situatie hoger dan bij gebruik van een papieren dossier. EPD-gebruik was geassocieerd met een reductie van de tijd tussen de start van de hiv-zorg en de eerste meting (baseline) van het aantal CD4⁺ T-cellen. EPD-gebruik was geassocieerd met een betere naleving van de pre-ART-richtlijnen die aanbevelen om iedere 6 maanden het aantal CD4⁺ T-cellen te meten. EPD-gebruik bevorderde de datakwaliteit. De datamanagers, die patiëntgegevens in het EPD invoeren, vormden een extra controlelaag voor de datakwaliteit en consulteerden de clinici wanneer ze tegen ontbrekende gegevens aanliepen.

In **hoofdstuk 4** zijn de resultaten beschreven van een multi-center voor-na studie naar de associatie tussen EPD-gebruik en de juiste initiatie van ART bij hiv-patiënten. De studie is uitgevoerd in dezelfde 17 zorginstellingen als uit hoofdstuk 3. We toonden aan dat EPD-gebruik was geassocieerd met een toename van de kans op het starten van ART onder daarvoor in aanmerking komende patiënten die hiv-zorg ontvingen. De duur tussen het moment waarop iemand in aanmerking komt voor ART en het moment waarop ART daadwerkelijk gestart werd was korter in de periode waarin het EPD gebruikt werd maar deze afname in tijd was niet statistisch significant. Factoren anders dan het gebruik van een EPD, zoals het gedrag van de zorgverlener, tijd om de patiënt voor te bereiden en de bereidheid van de patiënt zelf om te starten met ART, kunnen hiervoor verklaringen zijn. Het percentage patiënten in de studycentra dat in aanmerking komt voor ART en ook daadwerkelijk ART krijgt (80%) was hoger dan de WHO en de hiv/aids-programma’s van de Verenigde Naties (UNAIDS) in 2011 inschatten voor SSA (56%). Er is echter dus nog steeds 20% onderbehandeling. Om dit probleem aan te pakken en er voor te zorgen dat alle in aanmerking komende patiënten ook daadwerkelijk ART krijgen, zijn andere benaderingen voor het traceren en adviseren van patiënten nodig. Overbehandeling, d.w.z dat patiënten ten onrechte met ART zijn gestart, is in deze studie niet aangetroffen.

Om te leren van reeds uitgevoerde evaluatiestudies naar het effect van EPDs met BOS functionaliteit op de kwaliteit van hiv-zorg hebben we een systematisch literatuuronderzoek uitgevoerd naar originele
studies die de associatie tussen EPD met BOS functionaliteit en de kwaliteit van hiv-zorg onderzochten of die barrières voor de implementatie van dergelijke systemen in ontwikkelingslanden, inclusief SSA, beschreven. De bevindingen zijn beschreven in hoofdstuk 5. Twaalf studies werden geïncludeerd, tien daarvan werden uitgevoerd in SSA en twee in het Caribisch gebied. Slechts drie studies kwantificeerden de associatie tussen BOS en relevante uitkomst- en procesmaten zoals tijd tot aanvraag van CD4⁺ T-cell-test, wachtijd voor de patiënt en gemiste afspraken door de patiënt. Eén van de bevindingen van het systematisch literatuuronderzoek was dat BOS was geassocieerd met verbeterde datakwaliteit. Het merendeel van de studies liet zien dat de dataverzameling op papier plaatsvond en gegevens retrospectief werden ingevoerd in het EPD. Slechts één studie rapporteerde directe gegevensvastlegging tijdens het zorgproces. Implementatie van BOS en evaluatiestudies in ontwikkelingslanden zijn in het algemeen prematuur zoals te zien is aan de eenvoudige onderzoeksopzet van de studies in het literatuuronderzoek. Dit is opvallend gezien de grote investeringen van wereldwijde initiatieven om zorgsystemen te verbeteren in SSA. Het is belangrijk ons te realiseren dat het gebruik van EPDs en BOSen toeneemt door deze initiatieven.

Immunologisch behandelfalen onder hiv-patiënten kan optreden wanneer er een suboptimale reactie van het immuunsysteem op de ART optreedt. Met de toename van het aantal hiv-patiënten dat ART krijgt, kan een BOS potentieel nuttig zijn bij het detecteren van behandelfalen en het geven van suggesties aan zorgverleners omtrent het juiste klinische handelen. Hoofdstuk 6 beschrijft de bevindingen van een multi-center geclusterde RCT voor het evalueren van het effect van een EPD met BOS op het vroeg detecteren van immunologisch behandelfalen onder hiv-patiënten in 13 klinieken in de provincie Nyanza. Het BOS is gebaseerd op de WHO behandelrichtlijnen om immunologisch behandelfalen te detecteren en hierop de juiste acties te ondernemen. De studie laat zien dat er een relatie is tussen het gebruik van het BOS en de hogere kans op het juiste klinische handelen bij immunologisch behandelfalen. Er was een substantiële afname in de tijd tussen het immunologisch behandelfalen en het ondernemen van de juiste actie. Het BOS was tevens gerelateerd aan het sneller voorschrijven van een baseline CD4⁺ T-cel-test en het tijdig bepalen van volgende CD4⁺ T-cel metingen. Het aantal gedocumenteerde CD4⁺ T-cel-metingen was significant hoger in de klinieken waar het BOS was geïmplementeerd ten opzichte van de klinieken waar een EPD zonder BOS was geïmplementeerd.

Eerdere studies naar het effect van een EPD op de kwaliteit van hiv-zorg rapporteerden lage aantallen vastgelegde CD4⁺ T-cel-metingen. Er is dus ruimte voor verbetering met behulp van innovatieve benaderingen zoals een BOS. Hoewel onze studie aantoonde dat het BOS een effectieve interventie is, is er nog steeds aanzienlijke ruimte voor verbetering in het registreren van de behandelaacties die zorgverleners ondernemen. Voor bijna 45% van de patiënten bij wie de behandeling faalt is geen actie op dit falen geregistreerd. In de interventiegroep was het percentage patiënten met behandelfalen en daarop ondernomen actie significant hoger dan in de controlegroep (54.9% vs. 29.5%). Het gebrek aan geregistreerde gegevens heeft potentiële effect op de continuïteit van de hiv-zorg, met name in situaties waar patiënten door meerdere zorgverleners worden gezien. Het BOS beperkte zich in onze studie tot redenerregels om op basis van het aantal CD4⁺ T-cellen vast te stellen of een patiënt in aanmerking komt voor ART en voor het monitoren van de immunologische reactie op de hiv-behandeling. Voor andere klinische beslissingen, maar ook voor het bepalen of een patiënt in aanmerking komt voor ART, is ook informatie over diagnoses en klachten belangrijk. Om dergelijke beslisregels in een BOS te kunnen
opnemen, en om adviezen te genereren, moeten gegevens over diagnosen gestructureerd en gecodeerd worden vastgelegd. Andere barrières om BOSen te implementeren in ontwikkelingslanden zijn de zwakke infrastructuur, zoals onbetrouwbare elektriciteitsvoorzieningen en slechte computers, en uitdagingen ten aanzien van het personeel zoals laaggeschooldheid en gebrek aan computervaardigheden. Vergeleken met de westerse wereld zijn deze uitdagingen uniek voor ontwikkelingslanden, en deze gelden zeker in SSA.

**Hoofdstuk 7** beschrijft een gestructureerde aanpak voor het definiëren van een op SNOMED CT gebaseerde verzameling concepten van aids–definiërende ziekten (ADZ), en evalueren de dekking van SNOMED CT voor dit medisch domein op basis van ADZ die in een groot tertiair ziekenhuis in Kenia worden vastgelegd. Het uiteindelijke doel van de studie was om de datakwaliteit te verbeteren door gestandaardiseerde vastlegging van ADZ, gebruik makend van SNOMED CT, waarvan is aangetoond dat het de accuraatheid, compleetheid en herbruikbaarheid van gegevens kan verbeteren in de westerse wereld. Vanuit vier verschillende bronnen werden 1000 concepten, beschreven met bijna 1800 termen, geïdentificeerd. Bijna alle ADZ-concepten die in Kenia in de praktijk werden gebruikt konden in SNOMED CT worden gevonden. De verzameling SNOMED CT concepten en bijhorende termen werden als interface terminologie geïmplementeerd in OpenMRS, het EPD dat in veel ontwikkelingslanden wordt gebruikt. Hierdoor wordt het vastleggen van ADZ gestandaardiseerd en kan automatisch het door de WHO gedefinieerde klinische stadium worden afgeleid en aan de hand daarvan ook worden bepaald of de patiënt in aanmerking komt voor ART. Op basis van studies in andere landen verwachten we dat het gebruik van deze ADZ referentieset en interface terminologie zal leiden tot een betere datakwaliteit die accurate afleiding van de klinische stagering en daarbij behorende beslissingen over de behandeling ondersteunt.

De prevalentie van hiv is in Kenia het hoogste in de provincie Nyanza, waar we de EPD- en BOS-evaluatiestudies hebben uitgevoerd. In dit proefschrift hebben we aangetoond dat EPDs de kans op ART vergroten onder patiënten die daarvoor in aanmerking komen, wat positieve effecten zal hebben op hun uitkomst. Een grootschalig gebruik van EPDs impliceert dat er meer patiënten op tijd ART krijgen. Daarnaast zal het tijdig aanvragen van laboratoriumtesten voor het monitoren van de effecten van de behandeling de cliënt ondersteunen in het nemen van tijdige behandelmaatregelen. Patiënten die falen op de behandeling zullen sneller geïdentificeerd worden zodat de juiste acties (op basis van de richtlijnen) ondernomen kunnen worden.

SSA loopt achter in de adoptie en het gebruik van zorg-ict door uitdagingen zoals die zijn benoemd in de studies in dit proefschrift en in andere studies uitgevoerd in landen met beperkte middelen. Met het bewijs dat voortkomt uit onze studies omtrent de effectiviteit van EPDs en BOSen voor het verbeteren van de adherentie aan de richtlijnen, de datakwaliteit en de kwaliteit van hiv-zorg is er een gegronde reden voor verdere investeringen in het verbeteren van zorg-ict naast die door de US President’s Emergency Plan for AIDS Relief (PEPFAAR) en de Global Fund Against AIDS, TB and Malaria (GFATM). De studies beschreven in dit proefschrift zijn uitgevoerd in samenwerking met de US Centers for Disease Control and Prevention (CDC) en het Keniaanse ministerie voor volksgezondheid en de Kenya Medical Research Institute (KEMRI) om bewijs te genereren omtrent de rol van EPDs en BOSen bij het verbeteren
van hiv-zorg. Deze evaluatie is onderdeel van een ambitieus nationaal project waar in 600 zorginstellingen een EPD wordt geïmplementeerd.

Onze studies identificeren mogelijkheden en uitdagingen voor het implementeren van zorg-ict in landen met weinig middelen en beperkingen in de infrastructuur en personele capaciteit. Door het gebrek aan een betrouwbare elektriciteitsvoorziening is het onmogelijk om een EPD met BOS te implementeren in het directe zorgproces. De Keniaanse overheid zou moeten investeren in innovatieve methoden voor elektriciteit zoals wind en zonne-energie. Initiatieven van de Keniaanse overheid zoals het “Rural Electrification Program (REP)” dat gericht is op betrouwbare elektriciteitsvoorziening in ziekenhuizen en scholen in afgelegen gebieden, zal in de toekomst de problemen in veel zorginstellingen oplossen.

Onze literatuurstudie liet zien dat vanwege het beperkte aantal en de lage kwaliteit van de studies er weinig informatie en bewijs bestaat over de voordelen of problemen van EPD- en BOS-implementaties. Goed opgezette, betrouwbare evaluaties moeten relevant bewijs genereren en daarmee de beslissers kunnen informeren over de juiste investeringen in zorg-ict in omgevingen met specifieke uitdagingen m.b.t. zorg-ict-implementaties zoals in SSA. Onze studie naar het effect van een EPD met BOS op de vroege detectie van immunologisch behandelfalen en het juiste klinische handelen daarop t.b.v. patiënten die ART krijgen (hoofdstuk 6) is een eerste voorbeeld van een dergelijke betrouwbare evaluatiestudie.

Er is behoefte aan meer betrouwbare evaluatiestudies, zoals RCTs, die de relatie tussen EPD en BOS op andere proces- en uitkomstmaten voor hiv-zorg en andere chronische ziekten onderzoeken. Voordat deze studies plaatsvinden moet er prioriteit gegeven worden aan het verbeteren van de ict-infrastructuur, zoals internetverbinding, en de computerscholing van zorgverleners. Echter, als een BOS voorschrijft dat een bepaalde labtest moet worden afgenomen maar dit is vanwege het gebrek aan laboratoriumcapaciteit onmogelijk, dan zal het BOS geen effect teweeg brengen. Daarom verdienen ook verbeteringen van de algemene gezondheidszorgfaciliteiten zoals de capaciteit van medisch laboratoria grote aandacht.
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Dankwoord
When I made up my mind to find a world class PhD program that would equip me with skills to conduct high quality research, I spent many weeks reviewing websites of several universities in Africa, Europe and North America. University of Amsterdam (UvA) was to be my dream university and I thank several of the staff at the department of medical informatics without whom it would not have been possible to successfully complete my research studies at UvA and write this thesis.

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Tom Oluoch was born in Kisumu, Kenya on 10\textsuperscript{th} July 1969. He studied applied mathematics and computer science at undergraduate level and obtained a Bachelor of Science (BSc) degree at the University of Nairobi, Kenya in 1992. In 1997, he obtained a post-graduate diploma in Computer Science at the University of Nairobi after a year of full-time learning. He enrolled on a full-time Master of Science course at the University of Manchester, United Kingdom in 2001 and graduated with an MSc (Advanced Computer Science) in 2002. Since 2011, he has been pursuing a PhD in Medical Informatics at the University of Amsterdam, The Netherlands and is scheduled to defend his thesis in May 2015.

Tom worked for the BKH Consulting Engineers in Kisumu, Kenya as a systems analyst from 1993 to 1998 where he gained valuable experience developing database systems for monitoring the performance of a rural water project funded by the Dutch government. In 1998, he joined the Wellcome Trust/Kenya Medical Research Institute (KEMRI) research collaboration program as the head of the data management and ICT. He developed data management systems to support several research studies in one of the leading research institutes in Africa. He also led a team of data analysts and statisticians who provided data management and data analysis support for the research team. In addition, he was responsible for the ICT installations at the research center which included a local area network, VSAT communication, email and database servers and a helpdesk system. He left Wellcome Trust/KEMRI in 2005 to join the US Centers for Disease Control and Prevention (CDC) in Nairobi, Kenya as the Chief of Data Management.

From 2005 to date, Tom has provided leadership in data management and medical informatics at CDC and in Kenya. At CDC, he leads a team consisting of data managers, epidemiologists, statisticians and monitoring and evaluation advisors. He has led the implementation of large informatics projects, the latest being the national rollout of electronic medical records (EMRs) in Kenya and the integration of patient level information systems with aggregate reporting systems. He has also played a key role in a number of epidemiologic studies including the Kenya AIDS Indicator Survey which is a national, population-based survey on bio-behavioral factors associated with AIDS. He has conducted five evaluation studies and has published 15 articles on HIV epidemiology and medical informatics in peer-reviewed journals.

Tom is the founding and current chairman of the Kenya Health Informatics Association (KeHIA). KeHIA, which is affiliated to the International Medical Informatics Association (IMIA), brings together professionals from diverse backgrounds with an interest in health informatics. He previously served as the secretary to the board of management for the Consortium for National Health Research in Kenya and was responsible for health systems and informatics activities (2008 – 2012).