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Economic Evaluation of Rapid HIV Testing Approaches

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Acronyms and Abbreviations

ART	Antiretroviral Therapy
CADTH	Canadian Agency for Drug Technologies and Health
CEA	Cost Effectiveness Analysis
CEPAC	Cost-Effectiveness of Preventing AIDS Complications
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
Cr. I	Credible Interval
ED	Emergency Department
HIV	Human Immunodeficiency Virus
NMA	Network Meta-analysis
NRCT	Non-randomized Controlled Trials
QALY	Quality-Adjusted Life Years
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trials

Executive summary

Introduction

HIV testing is an important step in controlling the spread of HIV worldwide. Data from the UNAIDS suggests that about 50% of people living with HIV are unaware of their diagnosis. Canadian estimates suggest that about 25% of HIV infected persons are unaware of their status. Ontario specific estimates suggests that there may be close to 40,000 persons living with HIV in Ontario; however, 27,000 persons are known and documented to be living with HIV in Ontario. The importance of testing and early diagnosis is well documented with evidence demonstrating that early treatment improves outcomes both for infected individuals and the communities they live in. This premise forms the foundation for the highly effective “treatment as prevention” approach.

There are currently many HIV testing approaches including serum and saliva-based technologies. Testing can also be categorized based on duration to receipt of test result. With conventional HIV testing, results become available after greater than 24 hours. Rapid testing approaches such as rapid - facility based testing; rapid - location based testing; and rapid - mobile testing ensure results are available within 24 hours and in many cases, within a few minutes.

Effectiveness studies of individual approaches have been conducted, however, studies on the cost-effectiveness of the various approaches in Canada are presently lacking. Most of the available economic studies have been conducted in high prevalence low-income countries, and as such, are not entirely applicable to the Canadian experience.

Research objectives

The overall aim of the thesis is to investigate the program and performance effectiveness, as well as the economic evidence for the use of rapid HIV testing options compared with existing conventional testing options. To achieve this there were three specific objectives, namely:

i. To perform a systematic review of the available cost effectiveness evidence of rapid HIV testing approaches.

ii. To perform a second systematic review and determine relative effect estimates for the use of available rapid HIV testing approaches versus conventional approaches

iii. To determine the cost effectiveness estimates of the use of these testing approaches as they apply to a Canadian context.

Results

Rapid HIV Testing for improving uptake of HIV/AIDS services in people with HIV Infection - A Systematic Review and Network Meta-analysis

HIV testing has evolved to include rapid testing done in hospitals, non-clinical environments such as bathhouses, places of worship, learning environments and in other cases mobile HIV testing options have also been offered using mobile vans or other motorized vehicles. While there is overall evidence from systematic reviews and meta-analysis of the head-to-head benefits of rapid HIV testing compared to conventional HIV testing, there is insufficient evidence of the indirect benefits of the various types of rapid HIV testing based on location of the tests to identify if there is a differential benefit based on the location where the testing was conducted.

This study addressed this by conducting a systematic review and a network-meta-analysis of the HIV testing options. From 3329 articles, we included 4 randomised controlled trials and 1 cluster randomised controlled trial that compared conventional hospital-based HIV testing with rapid HIV testing options stratified by testing location and conducted both head-to-head and indirect testing comparison of these approaches. For our analysis we used RevMan and NetMetaXL respectively. We present our effect estimates as relative risks.

Our analysis showed that with direct head-to-head comparison, both facility and location based rapid voluntary counselling and testing (VCT) were associated with improvements in receipt of results (relative risk (RR) = 2.52; (95% CI: 1.33 to 4.75); and (RR = 1.76; 95% CI: 1.46 to 2.12) respectively.

Of note, head to head analysis from two studies including 83,825 subjects showed that rapid facility-based HIV testing was associated with increased HIV case finding among participants (RR = 1.90; 95% CI: 1.05 to 3.43). Heterogeneity between the two studies was low (I^2 = 0%; p = <0.0001). Finally, we note that the estimates derived from these indirect testing comparisons have wide confidence intervals.

The evidence from this review will be of interest to practitioners, researchers as well as policy makers reinforcing not only the clinical effectiveness of rapid HIV testing approaches but also the benefit of rapid location-based testing where this may result in its increased use in population-based HIV programming

Rapid HIV testing options versus conventional HIV testing: A systematic review of economic evaluations

A systematic review of economic evaluations of rapid HIV testing approaches versus conventional HIV testing in high income, low HIV prevalence settings was conducted. This review also assessed the methodologic quality of the included studies using the Drummond criteria and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

1524 records of English language studies were identified from which five articles satisfied the inclusion criteria and included in the review. The review showed that there was economic evaluation evidence to support the use of rapid HIV testing approaches. Estimates showed that rapid HIV testing options were associated with cost per quality adjusted life year (QALY) gained ranging from $42,768 to $90,498. Regardless of HIV prevalence, rapid HIV testing approaches continued to be the most cost-effective option.

Economic evaluation of HIV testing - A discrete event simulation

The third study was an economic evaluation to examine using Canadian cost estimates to estimate the clinical and economic benefits of the use of rapid HIV testing approaches as a population programming tool in low prevalence high income countries.

To achieve this, we developed a modified Centers for Disease Control staging for HIV progression based on CD 4 cell counts and clinical symptoms and applied the effect estimates obtained from the network meta-analysis conducted to meet the second objective. These estimates considered the relative effects of the various testing options. I

then applied disease stage costs and resource utilization estimates for a Canadian reference population.

The analysis was conducted from a public payer perspective and employed a discrete event simulation (DES) modelling approach model developed in Microsoft Excel to describe clinical progression of HIV patients diagnosed using different testing approaches over time. DES allows for modelling of the various patient populations that exists and accounting for the events (change in disease stages) that can happen differently between various patients.

Consistent with the recommendation of the Canadian Agency for Drug Treatments and Health (CADTH), the reference case analysis was conducted using a probabilistic analysis assigning probability distributions to input parameters and randomly selecting values for each parameter from their distribution. The results are presented as cost per person tested, and cost per quality adjusted life years (QALY) gained.

Our analysis showed that conventional HIV testing was the most expensive option at $879,019.67 and produced 29.49 QALY's, while the least expensive option was associated with the use of rapid hospital-based HIV testing at $878,977.47 also producing 29.49 QALY's. Both rapid HIV testing approaches were less expensive and produced more QALY's compared to the conventional hospital-based testing. We also found that a willingness to pay (WTP) threshold of $50,000, rapid hospital-based HIV testing was the most likely cost-effective testing option in 80% of replications and the cost effectiveness of rapid hospital-based testing continued at higher thresholds of willingness to pay.

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Finally, to Him who was, who is and is to come, I owe it all to you. To you be honor and glory.

CHAPTER ONE

Rapid HIV testing: Evolution and benefits

Introduction

In Canada, the Public Health Agency of Canada estimates that of the approximately 80,000 people believed to be living with HIV/AIDS in Canada to the end of 2011, about a quarter were unaware of their HIV infection. These estimates are consistent with estimates from other low prevalence, high income countries where undiagnosed cases of HIV are estimated to account for 21-30 percent of the HIV infected population (1).

With this proportion of infected persons unaware of their disease status, this could constitute a pool of persons who can continue to transmit disease thereby hindering the goal of ending the HIV epidemic as outlined UNAIDS 90-90-90 document (2).

To bridge this gap, various interventions have been implemented in various jurisdictions to increase the testing rates and numbers. These include including increased access to HIV testing, self-testing, provider- initiated counselling and testing and the use of rapid HIV testing approaches.

History of HIV testing

HIV testing has evolved significantly over the years from the first-generation assays that only detected IgG antibody to HIV-1 only.

HIV was first isolated in 1983 and described as the virus associated with AIDS. The earliest first generation tests developed in 1985 were sensitive but had an antibody-negative window of up to 12 weeks or more post-infection and were associated with false positive results particularly in low-risk individuals (3,4). Due to the tendency to provide false positive results, a second level of testing was required to increase the

specificity of the tests and this was achieved using the Western Blot and Human T-Cell Leukemia Virus (HTLV III) immunofluorescence assay.

Second generation HIV tests were developed in the late 1980's and these had improved specificity and the positive predictive values was also improved enhancing its use in low prevalence settings. Another benefit of these second-generation tests was the reduction of the antibody-negative window to 4 to 6 weeks following an infection. Third-generation tests reduced the antibody-negative window to about two weeks but still required a confirmatory test using either WB or IFA.

More recent HIV tests with sensitivity and specificity approaching 100% are now able to detect both HIV antibody and the HIV-1 p24 antigen providing separate results for each (3,4). These tests also have reduced antibody-negative detection windows of about two weeks making it easier to identify early infections and further reduced false positives. See Table 1.

Table 1: Schematic representation of the 30-year evolution of HIV diagnostic assays

Year	1985	1987	1991	1997	2015
Generation	1st	2nd	3rd	4th	5th
Antigen source	Virus infected cell lysate	Lysate & recombinant	Recombinant and synthetic peptides	Recombinant and synthetic peptides	Recombinant and synthetic peptides
Specificity	95 - 98%	> 99%	> 99.5%	99.5%	99.5%
Sensitivity	99%	> 99.5%	> 99.5%	> 99.8%	100%
Detects antibody and antigen	IgG Anti HIV-1	IgG Anti HIV-1 and IgG Anti HIV-2	IgG Anti HIV-1 and IgG Anti HIV-2 and Group O	IgG Anti HIV-1 and IgG Anti HIV-2 and Group O. Also detects HIV p-24 Ag	IgG Anti HIV-1 and IgG Anti HIV-2 and Group O. Also detects HIV p-24 Ag
Results	Single result	Single result	Single result	Single result; does not differentiate Ab from Ag positivity	Separate HIV-1 and HIV-2 Ab and Ag results
Confirming tests	HIV-1 western blot (WB) or immunofluorescence (IFA)	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1 WB or IFA, HIV-2 ELISA and WB if HIV-1 confirm is negative	HIV-1, 2 differentiation assay followed by qualitative HIV-1 RNA PCR if differentiation assay is negative	Not determined at publication

Source: Alexander TS. Human Immunodeficiency Virus Diagnostic Testing: 30 Years of Evolution. Clinical and Vaccine Immunology. 2016: 23(4); 249-253

With prophylactic and therapeutics treatment advances to address instances of occupational and non-occupational blood or body fluid exposures and the need to provide HIV results to patients in a clinic or emergency room or during labor and delivery, researchers and manufacturers developed rapid HIV assays.

Rapid HIV assays provides results in as little as 20 minutes usually with a finger prick method and are associated with a high degree of sensitivity. The sensitivity and specificity of these approaches approach those of traditional testing approaches.

There are a few similarities and differences between conventional HIV tests and rapid HIV testing approaches, and these are described in the table below.

Table 2: General and operational characteristics of conventional and rapid HIV tests

	ELISAs	Rapid tests
Detection (sample type/specimen)	HIV antibodies in plasma/serum	Several can detect HIV antibodies in whole blood (finger prick samples) as well as serum/plasma and saliva
Test accuracy[i]	Depending on the test Similar diagnostic performance of ELISA and rapid tests	
Laboratory equipment	Micropipette, washer, incubator, spectrophotometer	None to minimal
Laboratory personnel	Skilled laboratory technician	Can be performed by any health care worker who has been adequately trained, including counsellors.
Ease of performance[ii]	Level 4	Level 1 - 3 depending on test type
Time to perform test	Greater than two hours	Most 10 - 30 minutes
Shelf life	Usually 12 months	
Storage conditions	2 - 8°C	Some 2 - 8°C; most 2 - 30°C.

Adapted from WHO, CDC. 2004. Rapid HIV tests: Guidelines for use in HIV testing and counselling services in resource-constrained settings

Advantages of rapid HIV tests

These rapid approaches have been found to have advantages compared to conventional approaches. Two major advantages of rapid HIV testing are its portability and the associated short run-time providing test results in less than two minutes. Other

[i] Refers to test properties including sensitivity and specificity
[ii] Level 1: Little or no laboratory experience required; Level 2: Reagent preparation required; procedure has multiple steps; Level 3: Specific skills required, such as making dilution series or interpretation of agglutination patterns; Level 4: Trained laboratory technician and complex laboratory equipment required.

advantages include improved test uptake within the population, client preferences, improved receipt of test results, and the ability of these approaches to result in client diagnosis earlier in the disease progress (1,5–8).

It should be noted that a positive rapid HIV test is not considered final diagnosis. There is the requirement to send a sample of the client's blood to a public health laboratory for confirmatory testing. This can take up to a week however in the interim, given the high test accuracy of these kits the client is connected and engaged to care and treatment programs.

In Canada, there is only one rapid HIV screening test approved. This is an antibody test known as the INSTI test (9). Saliva or oral-fluid testing is not currently approved for use in Canada. The Public Health Agency of Canada reports that the use of oral fluids for HIV diagnosis is associated with higher rates of false negative results when self administered compared to health care worker administered testing (10). A systematic review comparing the accuracy of a oral versus whole-blood specimens in point of care HIV testing found that while oral test kits had high positive predictive values in high prevalence settings, they had lower sensitivity and PPV in lower prevalence settings (11) Two other studies in high prevalence settings also showed reduced sensitivity of oral fluid based HIV testing compared to serum based testing. Luo et al (12) studying a longitudinal Nigerian cohort using a Food and Drug Administration (FDA) approved oral fluid kit found that there was a delay of 29 days in diagnosis of seroconversion compared to plasma HIV testing.. Sherman et al (13) also used an FDA approved saliva

HIV test kit and found that compared to plasma testing, saliva kits had a lower sensitivity (81.5%) (13)

Finally, this thesis has three objectives. First, I will conduct a systematic review and indirect testing comparison to determine the relative effect estimates of available rapid HIV testing approaches compared to conventional approaches. The second objective would review the available cost effectiveness evidence of rapid HIV testing approaches and the final objective is to determine through an economic evaluation the cost utility estimates of these testing approaches in a Canadian context.

CHAPTER TWO

Rapid HIV Testing for Improving Uptake Of HIV/AIDS Services in People with HIV Infection - A Systematic Review and Network Meta-Analysis

Title: Rapid HIV Testing for Improving Uptake Of HIV/AIDS Services in People with HIV Infection - A Systematic Review and Network Meta-Analysis

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Type of article: Original research

Abstract

Background: Early HIV diagnosis is important for HIV programming and rapid HIV testing approaches have been shown to improve outcomes however it is unclear what form is most effective. This review assesses the effects of the various rapid HIV testing strategies sub classified based on location of testing into facility based; location based; and mobile HIV testing compared with conventional healthcare facility-based testing. **Methods:** We searched PubMed, Medline, Embase, Global Health, PsychInfo, Cochrane CENTRAL, Cochrane HIV/AIDS Group Specialized Register, conference abstracts and grey literature between 2001 to 2019 for English language experimental studies that compared various forms of rapid voluntary counselling and testing (VCT) with conventional testing among people at risk for HIV exposure. Data was extracted using standardized forms. Outcomes of interest were uptake of testing; receipt of results; HIV repeat testing; HIV incidence; and entry into HIV care and treatment programming. Direct and indirect comparisons were done using RevMan and NetMetaXL respectively. **Results:** Four published randomized controlled trials and one cluster randomized controlled trial. Facility and location based rapid VCT were associated with improvements in receipt of results (relative risk (RR) = 2.52; (95% CI: 1.33 to 4.75); and (RR = 1.76; 95% CI: 1.46 to 2.12) respectively. Indirect comparisons were associated with wide credible intervals.

Conclusion: Rapid location-based testing is associated with improved program outcomes compared to other options. Our estimates are associated with a significant

amount of uncertainty and would benefit from further research. PROSPERO ID: CRD42017039764

Introduction

Human Immunodeficiency Virus infection (HIV) is a blood-borne viral illness responsible for significant morbidity and mortality in Canada and the rest of the world. The Public Health Agency of Canada report estimated there were approximately 63,110 persons living with HIV (PLWHIV) (including AIDS) in Canada in 2016 (14). Of these, 14% were unaware of their infection and this was attributed to a number of factors including a lack of access to testing services, concerns about test confidentiality in rural settings and on reserve and an unfamiliarity with the health care system (6,14,15). Continued pockets of undiagnosed HIV infected persons in the community represents a significant public health challenge providing a source for continued transmission (16–18). Across various jurisdictions, this proportion ranges from about 26% in the United States in 2003 to about 14% in 2016 (19). Canadian estimates have declined to current rates from about 25% in 2012 and the United Kingdom reports about 25% of infected persons who are unaware of the presence of the disease (20,21).

These reductions have been achieved in part due to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 strategy, a three-pronged approach with the goal of ending the AIDS epidemic. The three component parts are ensuring that by 2020, 90% of all people living with HIV will know their HIV status; 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will experience viral suppression (2).

HIV-positive individuals who are commenced on antiretroviral therapy (ART) early in the disease process have significantly reduced transmission risk to uninfected partners and

have lower morbidity and mortality rates than those in whom treatment is delayed (21–23). Recognizing the risks due to undiagnosed HIV cases, UNAIDS developed the "Getting to Zero" strategy (24). The strategy is based on three major areas namely: revolutionizing HIV prevention; catalyzing the next phase of treatment; and advancing human rights and gender equality for the HIV response. The first of these areas focuses on "*fostering political incentives for commitment and catalyzing transformative social movements regarding sexuality, drug use and HIV education for all, led by people living with HIV and affected communities, women and young people*". Additional consideration was also given to ensuring equitable access to cost-effective HIV prevention programmes (24).

HIV counseling and testing is one of the pillars of HIV prevention and this was reinforced by the U.S. Preventive Services Task Force recommendation suggesting that nearly everyone between the ages of 15 - 65 be screened for HIV (16,23,25). In Canada, the HIV screening and testing guide recommends that discussion of HIV testing be a component of routine medical care, and further recommends that HIV testing be normalized. The choice of HIV testing approaches available for use varies. They can be classified based on location of testing, testing sample used as well as time interval to receiving results. The most common form is healthcare facility blood-based testing commonly referred to as conventional HIV testing. Other options based on a mix of location-sample types are saliva-based HIV testing and pin-prick blood drop-based testing. The non-healthcare facility based approaches can be conducted in a variety of locations such as home-, work- parole office-, peer- and community-based (CB)

voluntary counselling and testing (VCT), mobile testing and universal population testing (16,26–28).

Previous reviews evaluating the effect of rapid HIV tests have considered these approaches as a homogenous entity however there are potential differences in the effects of these approaches due to ease of reaching and engaging harder to reach or marginalized populations (16).

This review assesses the effects of the various rapid HIV testing strategies on the following HIV testing outcomes: uptake of testing; receipt of results; HIV repeat testing; and HIV incidence; compared to conventional laboratory testing approaches. Rapid strategies are sub classified based on location of testing into facility-based HIV testing; location based; and mobile HIV testing. Examples of locations are homes, social locations such as houses of worship, bath houses.

The specific objectives of this review are to:

- critically review and synthesize uptake of testing evidence on rapid compared to conventional laboratory HIV testing approaches;
- summarize the evidence on randomized, controlled trials (RCTs) that have evaluated rapid HIV testing treatment; and
- present a comparison of the relative effect estimates of different HIV testing approaches.

Methods

Search methods

We searched electronic databases including PubMed, Medline, Embase, Global Health, PsychInfo, Cochrane CENTRAL, Cochrane HIV/AIDS Group Specialized Register, abstracts of important meetings (e.g. International AIDS Conference), AIDS specialty journals. We contacted experts for unpublished research and trials along with trial registers of HIV/AIDS Cochrane Centre and the Cochrane Infectious Diseases review group. All database searches were done with a time restriction from January 1, 2001 - July 31, 2019 and limited to English language studies. This review was registered in the PROSPERO database (CRD42017039764). This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Equity Extension (PRISMA-NMA) 2015 (29). See Appendix 1 for PRISMA-NMA checklist.

Study selection and data abstraction

Two reviewers (OM, OO) screened titles and abstracts independently using pre-specified inclusion criteria. Articles considered relevant and agreed on by both reviewers were retrieved in full text. Where there were any disagreements, this was resolved by discussion between OM and OO. When consensus was not reached, a third party (KP) was involved in the resolution. Two reviewers (OM and OO) conducted independent data extraction using a pre-tested data extraction form, as recommended in the Cochrane handbook (30).

Eligibility criteria

Types of studies

We included study designs recommended by the Cochrane Effective Practice and Organization of Care review group: randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs) controlled before-after studies, interrupted time series studies, and cohort studies with control groups. Full economic evaluation, cost analyses and comparative resource utilization studies were excluded.

Types of participants

All persons tested for HIV were eligible, as well as our key populations who are at high risk for exposure to HIV. These key populations are: people from HIV concentrated endemic populations with prevalence >1%, Aboriginal peoples, youth, pregnant women, men who have sex with men (MSM), injection drug users, ethnic minority groups, sex-workers and also those who had repeatedly tested HIV negative in the past (31). We limited participants to persons older than the age of maturity (18 years) in most Canadian provinces (32)

Types of interventions

We considered of the following HIV rapid testing studies. Rapid facility based testing (where facility refers to health care facility); rapid location based; and rapid mobile testing compared with conventional (serum-based) laboratory testing approaches. We excluded studies that considered saliva-based tests due to concerns about test performance (12,33). Saliva based HIV testing when self-administered had a lower sensitivity compared to health professional administered tests (10–13,33).

Types of outcome measures

The primary outcomes considered in this update are uptake of testing; receipt of results; HIV repeat testing; and HIV incidence. We chose these outcomes because they are considered important to the clinical outcomes in patients.

We did not consider the effect of HIV related stigma because of findings from a previous study that found there was already a floor effect in the prevalence of HIV related stigma (16,34).

Where available, we extracted data on potential harms, result-related anxiety and relational conflicts.

Risk of bias

Risk of bias was appraised by two reviewers using the EPOC criteria for randomized controlled trials (RCT), controlled before-after (CBA) studies and interrupted time series (ITS). (35). Any disagreement was resolved by consensus, or involvement of a third party, if necessary.

Statistical analysis

The statistical summary analysis of the studies was done in two stages. We conducted a head-to-head comparison of the various HIV testing approaches identified in the studies aggregating the data for each outcome using a random effects model. The random effects model for meta-analysis weights the studies relatively more equally than a fixed-effect analysis in the presence of heterogeneity(30).

The next phase was the conduct of indirect testing comparisons where there are no head-to-head trials. Like the earlier phase, a random effects model was also used in the

network meta-analysis of the data allowing for a more equal weighting of the studies (30).

The head to head comparisons was done using Review Manager (RevMan; Cochrane Collaboration), version 5.2.3. Indirect analysis was conducted using a Microsoft-Excel based tool called NetMetaXL tool programmed in Visual Basic for Applications (36,37). This provides an interface for conducting Bayesian network meta-analysis using WinBUGS from within Microsoft Excel (36).

The models were implemented in a fully Bayesian framework using the NetMetaXL with posterior distributions based on 10,000 samples after a burn-in period of 10,000 iterations. Convergence was assessed by visual examination of parameter chains and the Gelman - Rubin diagnostic (13). Models were compared via the deviance information criteria (14). Summary statistics and odds ratios with 95% credible intervals (Cr. I's.) were obtained from the posterior distributions produced.

Results of head to head comparisons are presented as odds ratios with 95% confidence intervals and results shown using forest plots while the results for the indirect comparisons are presented in a league table.

Assessment of heterogeneity

Study heterogeneity was assessed in three ways: 1) clinical heterogeneity in the population, intervention, comparison, outcomes and settings; 2) visual inspection of forest plots for heterogeneity; 3) use of the chi-squared test for heterogeneity ($p<0.2$) and the I-squared test (using the criterion of >70% for heterogeneity).

Sensitivity analysis

We assessed the robustness of results by evaluating for each outcome which results were based on studies at low risk of bias for that outcome, and by using the risk of bias grid of Review Manager.

Results

A total of 3329 abstracts and titles were retrieved and reviewed by our searches of the databases. After screening, five studies including three RCTs and two from a recent meta-analysis were identified for inclusion in our study (38–42). The flow of the literature search through the review is presented in Figure 1. Basic characteristics of the study settings and populations are set out in Table 3.

Overall, there were about 100,000 participants. One study was a cluster randomized trial where general practices in the United Kingdom were randomly assigned to offer rapid facility based HIV testing or the usual standard of care (39). A second Australian study randomized MSM to either receive rapid facility based HIV testing obtained with finger prick blood drop or to conventional HIV serology using the facilities standard testing approach (41). The third RCT considered three testing approaches namely the intervention arms of nurse-initiated screening, conventional counselling and testing; nurse-initiated screening, streamlined counselling and rapid facility based testing compared with the conventional testing option (43).

One of the trials was conducted in a sexually transmitted disease (STD) clinic in the US where participants were randomized to either rapid facility based testing or standard

counseling testing (40). The last study was a multi-arm randomized trial conducted in a variety of settings including needle exchange facilities and bath houses used by MSM (42).

The interventions considered by Spielberg et al were conventional test with standard counseling; rapid location-based test with standard counseling; oral location-based test fluid test with standard counseling; and conventional test with choice of written materials or standard counseling (42).

The network geometry is shown below with each treatment node representing the intervention as labelled and weighted according to the number of participants who received the particular intervention with the sizes of the nodes corresponding to the sample size.

Figure 1: Network geometry of included studies

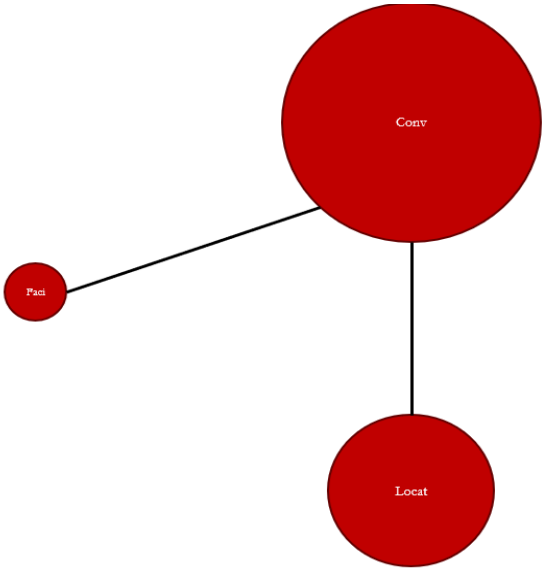


Figure 2: Selection of studies for inclusion in the review

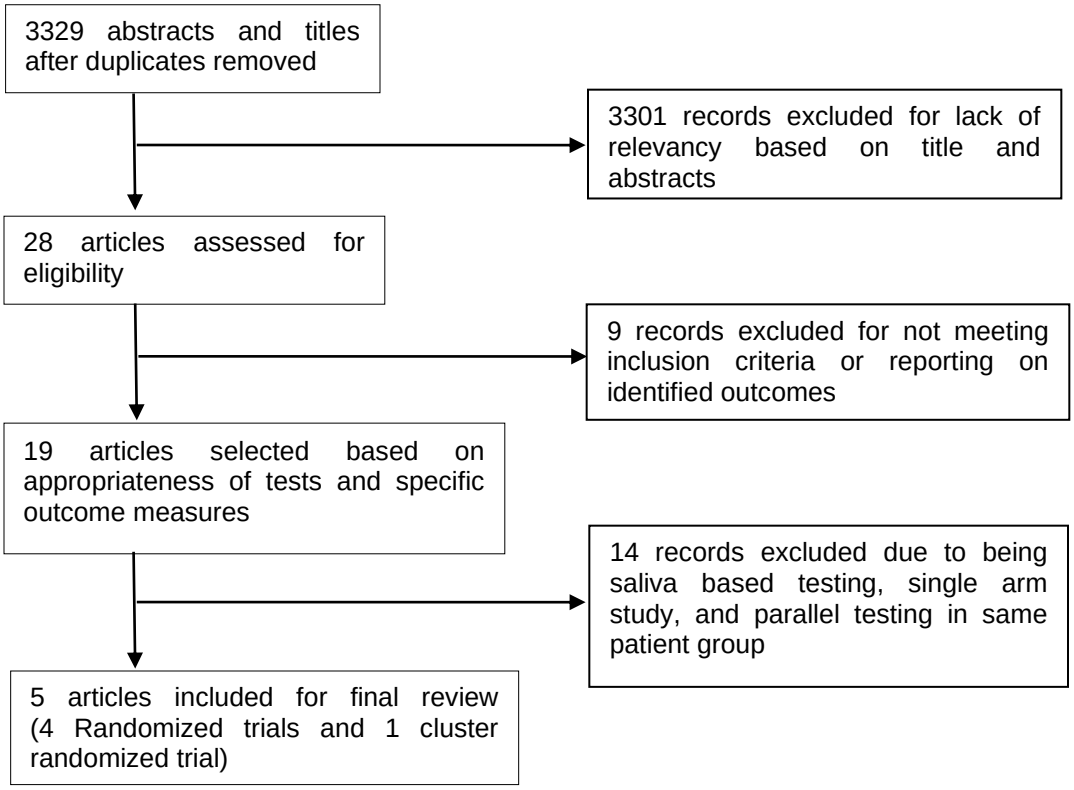


Table 3: Summary of included studies: population characteristics

Authors	Title	Study type	Study country	Study setting	Interventions	Control arm	Outcomes
Anaya et al	Improving HIV screening and receipt of results by nurse-initiated streamlined counseling and rapid testing.	RCT	United States	Large veteran affairs clinic	Nurse-initiated screening, conventional counselling and testing; Nurse-initiated screening, streamlined counselling and rapid testing	Conventional Counselling and Testing	HIV testing rates, HIV result receipt, Sexual risk reduction, HIV knowledge improvement
Leber et al	Promotion of rapid testing for HIV in primary care (RHIVA2): a cluster-randomized controlled trial	Cluster-RCT	United Kingdom	General practices in a multiethnic, socioeconomically high HIV prevalence London borough	Rapid HIV testing with £10 per completed test	Usual care with offer of serology and following patient request	CD4 count at diagnosis
Metcalf et al	Relative efficacy of prevention counseling with rapid and conventional HIV testing: A randomized, controlled trial (RESPECT-2)	RCT	United States	STD clinics	Rapid HIV testing and counseling in 1 visit	Conventional HIV testing and counseling in 2 visits	STDs including HIV within 12 months of interventions[iii]

[iii] STD incidence was measured using the combined results of tests for gonorrhea, chlamydia, trichomoniasis, syphilis, and HIV infection

Read et al	Provision of rapid HIV tests within a health service and frequency of HIV testing among men who have sex with men: a randomized controlled trial	RCT	Australia	Public sexual health service	Rapid finger prick HIV testing	Conventional HIV serology	Incidence rate of HIV testing (Number of tests per person per year)
Spielberg et al	Choosing HIV Counseling and Testing Strategies for Outreach Settings - A Randomized Trial	RCT	United States	Needle exchange programs; MSM bathhouse	Rapid VCT	Conventional VCT	Results receipt rate

Risk of bias

All studies reported adequate randomization. Two studies by Leber et al and Metcalf et al provided specific statements about allocation concealment however no other studies offered explicit statements about allocation concealment (39,40). The risk due to blinding study participants and personnel was mixed across studies with one of the studies considered at high risk given the nature of the intervention that makes blinding impractical for participants however this was implemented for personnel in some of the studies. We considered four of the studies low risk with respect to the risk due to incomplete outcome data and thus do not think the lost to follow-up rates across studies was significant to contribute to the risk of bias in our analysis (See Table 4) (40–43).

Table 4: Risk of bias assessed using the Cochrane Risk of Bias Tool

Study ID	Random sequence generation	Allocation concealment	Performance bias[iv]	Detection bias[v]	Attrition bias[vi]
Anaya et al	Unclear	Unclear	Low risk	Unclear	Low risk
Leber et al	Low risk	Low risk	High risk	High risk	High risk
Metcalf et al	Low risk	Low risk	Low risk	Low risk	Low risk
Read et al	Low risk	High risk	Low risk	Unclear	Low risk
Spielberg et al	Low risk	High risk	Low risk	Unclear	Low risk

Uptake of testing

[iv] Blinding of participants and personnel

[v] Blinding of outcome assessment

[vi] Incomplete outcome data

Metcalf and Leber reported on this outcome. We would have liked to use uptake of testing for inclusion in a head-to-head comparison, however, it was not possible because the data for the uptake of testing among the participants in the conventional testing arm of the study by Leber et al. (39,40) was unavailable. Metcalf et al. conducted a study in three public sexually transmitted diseases (STD) clinics in the United States. In this study, all participants were tested for HIV at enrolment and this may explain the parity of the analysis with a RR = 1.00; (95% CI: 0.99 - 1.01) when rapid facility-based testing was compared to conventional HIV testing.

Receipt of results

Three studies reported receipt of result outcomes using three testing approaches. This permitted head-to-head comparisons and indirect testing comparisons (41–43). The results show that compared to conventional HIV testing, rapid facility-based testing was associated with almost three-fold increased likelihood of participants receiving the test results with relative risk (RR) = 2.52; (95% CI: 1.33 - 4.75). Heterogeneity between the two studies was high (I^2 = 91%; p = 0.0008). See Figure 3. We postulate that the high heterogeneity in this analysis was due to the studies being conducted on two continents and involving different population groups.

When rapid location-based testing was compared to conventional testing, rapid location-based testing was associated with increased likelihood of receipt of RR = 1.76; (95% CI: 1.46 - 2.12). Heterogeneity was low (I^2 = 0%; p = 0.58). See Figure 3. This was a single study that was conducted in two settings: a needle exchange facility and a bathhouse.

Figure 3: Forest Plot of rapid facility-based HIV testing versus conventional testing on receipt of test results

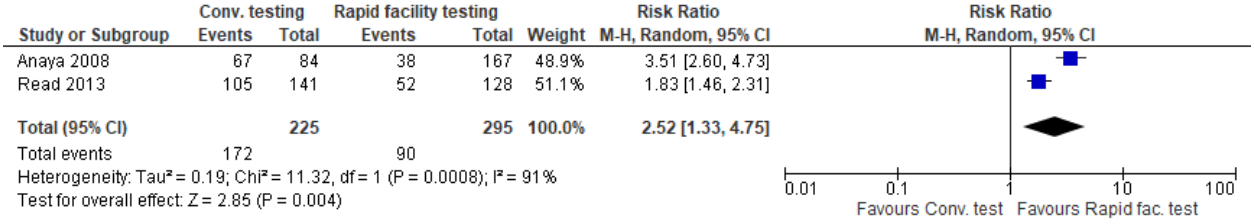
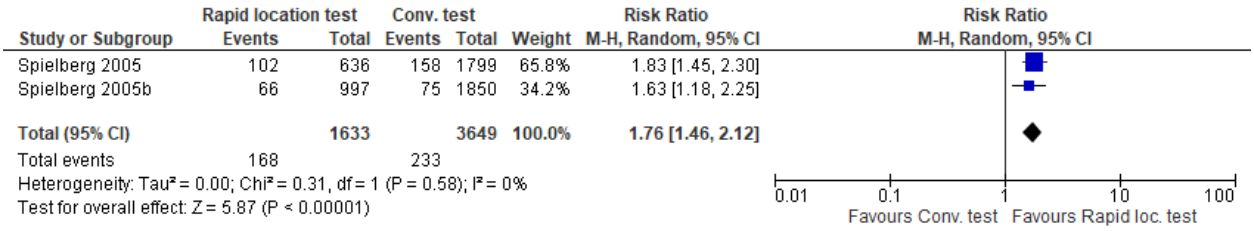


Figure 4: Forest Plot of rapid location-based HIV testing versus conventional testing on receipt of test results



Indirect testing comparison of the three testing options namely rapid location based, rapid facility based, and conventional healthcare facility-based testing was conducted. This was from three studies and involved 5802 participants (41–43). Studies did not have any multi-arm comparisons, there were two pairwise comparisons with direct data available.

As shown in Figure 5 and 6 below, compared to conventional testing, the other two approaches were associated with increased odds of receipt of test results. When the two rapid HIV testing approaches were considered, the odds of receiving test results after testing was higher when the tests were conducted in locations other than health care facilities. It is important to note the wide credible intervals of the measures of

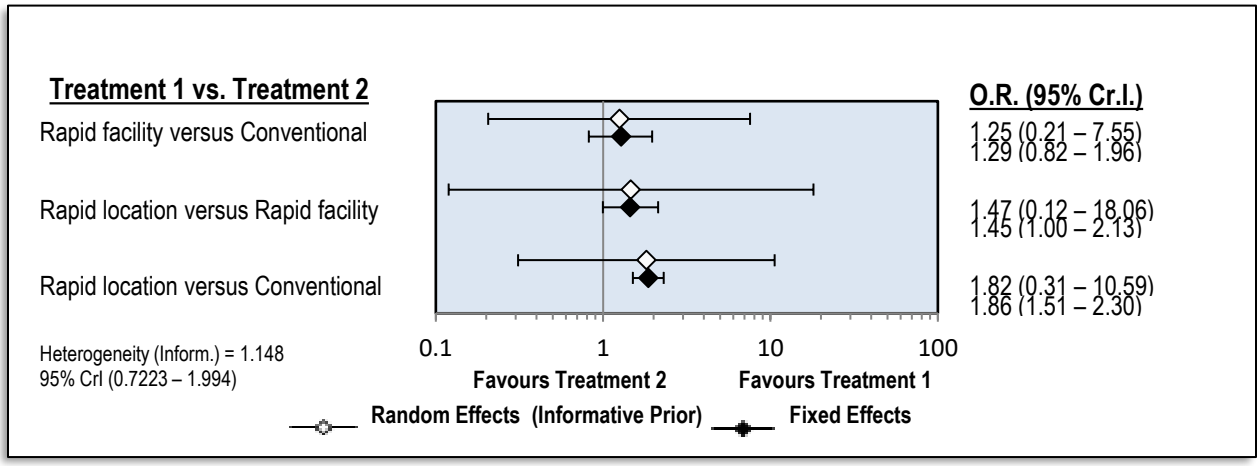
association used in this analysis. The results in the league table below are presented as random effects with informative priors models while the forest plot shows estimates using a fixed effects model.

Figure 5: League table of comparative effectiveness of three HIV testing approaches on receipt of test results

Rapid location		
1.47 (0.12 – 18.06)	**Rapid facility**	
1.82 (0.31 – 10.59)	1.25 (0.21 – 7.55)	**Conventional**

Using a fixed effects model in the forest plot, results in narrower credible intervals and this reinforces the conclusions from the earlier league table that rapid location-based HIV testing was associated with better odds of receipt of test results with odds ratio (OR) = 1.86; (95% Cr.I. :1.51 - 2.30).

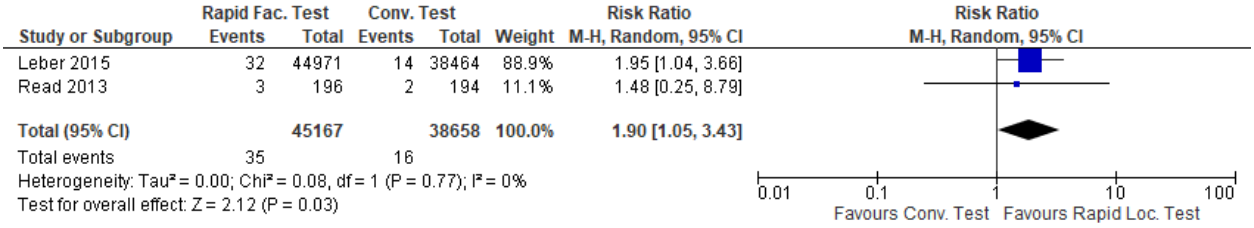
Figure 6: Forest plots showing the comparative effectiveness of three HIV testing approaches on receipt of test results



HIV Case Finding**Error! Bookmark not defined.**

Only two studies reported this outcome and thus only head-to-head comparison is possible. Our analysis showed that rapid facility-based HIV testing was associated with increased HIV case finding among participants. RR = 1.90; (95% CI: 1.05 - 3.43). Heterogeneity between the two studies was low (I^2 = 0%; p = <0.0001).

Figure 7: Forest plot of rapid location-based HIV testing versus conventional testing on HIV case finding



CD 4 count at diagnosis

Only one of the included studies considered the CD 4 count at diagnosis as an outcome (39). Leber et al found that the mean CD4 count was marginally higher in the intervention (rapid testing) arm compared to the control (conventional testing) arm at 356 cells per µl [SD 254] vs 270 cells per µl [SD 257]. The reported adjusted difference in square root of transformed CD4 count was 3·1, 95% CI -1·2 - 7·4; p = 0·16.

Visual assessment of the NMA plots compared to the meta-analysis plots shows consistent improved outcomes with the rapid HIV testing options. Finally, we were unable to conduct a sensitivity analysis for the various study outcomes due to limited number of eligible studies and participants.

Discussion

Our systematic review and network meta-analysis covers a good portion of the cascade of HIV care from uptake of testing to initial CD 4 count at diagnosis (44). We have been able to demonstrate the effectiveness of rapid HIV testing compared to conventional testing approaches. While we were unable to quantify the impact of rapid HIV testing on uptake of testing, a recent meta-analysis demonstrated the benefit of rapid approaches and found it was associated with a three-fold increase in the uptake of HIV testing (16).

The earliest and most common testing approach is the conventional HIV testing that involves ordering an HIV blood test requiring the patients return for results. A major drawback of this approach is that it has not performed well within marginalized communities(1,45). In Canada, these marginalized communities consist of persons at high risk for HIV exposure like persons who inject drugs, MSM, persons from HIV epidemic countries (prevalence >1%), street youth, pregnant women, sex workers, low-income and socially disadvantaged people, Aboriginal persons, and other minorities (45).

Rapid HIV testing options usually do not need whole blood for testing and usually make results available within a few minutes thus offering a more convenient testing choice and eliminates the need for clients to return later for results and thus expected to enhance testing rates and receipt of results. It is suggested that these approaches would be especially valuable in reaching marginalized populations(23). Available evidence also indicate that HIV infected persons after learning of their status reduce risky sexual behaviors and secondarily prevent disease transmission(23,46).

Conversely, among non-infected persons, knowledge of serostatus is likely to encourage healthy sexual behavior to prevent infections (16,46,47).

Previously, it was assumed that there was no impact in the reduction of HIV incidence among populations exposed to increased awareness of HIV status following increased and facilitated HIV testing. However, a recent multi-country cluster randomized study demonstrated a reduction in HIV prevalence following implementation of rapid HIV testing compared with standard HIV testing over a 36 month period(23,48). Sweat et al report consistent reduced HIV case finding associated with rapid community based VCT across three countries (48).

Our review sought to assess the comparative effectiveness of the various types of rapid HIV testing and specifically we found that it was associated with increased likelihood of receipt of results by clients. Regardless of testing approach, it was found that rapid testing options were more effective. The network meta-analysis further showed that when tests are done at locations where the target population are located such as in bathhouses or needle exchange facilities or other similar locations, the impact on receipt of test results is higher. This was consistent with evidence from other researchers that demonstrated increased uptake of testing, receipt or results and HIV incidence (34,48–50).

We also hypothesize that increase uptake and receipt of HIV test results is associated with increased level of knowledge about each individual's disease status and secondarily a possible proxy for level of health knowledge. We make this assumption because Coates and Sweat in their multi-country cluster randomized trial found that

rapid HIV testing was associated with improved behavior change and prevention particularly in individuals with HIV engages in high risk sexual activities. Specifically, the number of sexual partners of HIV-positive participants was associated with any 8% reduction (95% CI 1 - 15; p=0·034), and in HIV- positive men there was a reduction in the number of partners by 18% (95% CI 5 - 28; p=0·009)(34,48,49).

The hypothesis apriori was that rapid HIV testing resulted in increased testing levels, resulting in earlier diagnosis of persons when the disease impact on the immune system as measured by the CD 4 count is not severe thus resulting in better treatment outcomes. This hypothesis was confirmed in this review showing that the CD 4 counts of participants was higher in the rapid facility testing arm compared to the conventional approaches. The availability of only one study measuring this outcome may be related to the requirements of the tests that is usually beyond what may be done with relative ease of rapid HIV tests. Nonetheless, this provides further evidence that rapid testing is associated with earlier diagnosis and potentially improved treatment outcome.

Our review also shows the relative benefit of rapid HIV testing approaches and specifically, the impact of rapid location-based testing on receipt of test results as a core step in the care cascade. This provides further evidence to support this intervention as a population health intervention (39–43). It is also important to highlight that these findings are consistent with the existing body of literature.

While this evidence about the impact of receipt of results is from a limited number of studies, we consider it very important as it suggests that providing tests to target populations at locations where they conduct social activities is highly effective and

serves to remove a barrier in accessing care. Providing access at these types of locations is consistent with principles of harm reduction such as pragmatism and low threshold for accessing services (51).

Our review used a rigorous and transparent systematic review method, with an a priori protocol. We included studies from three continents (Europe, Australia and North America) encompassing diverse population groups including high-risk populations, low-income populations as well as the general population. The decision to include these three jurisdictions was because of they all had some form of publicly funded health care system, similar HIV epidemiology and close economic indices. This review also addresses some of the concerns identified in a previous review about the inability to individually assess the impact of rapid tests conducted in a variety of settings such as community and health facility settings (16).

This review as far as we are aware presents the first indirect testing comparison of the various rapid HIV testing options compared to conventional HIV testing. Previous reviews have considered direct head-to-head comparisons (16,25,27,52). While the estimates obtained from the network meta-analysis have wide credible intervals, these are clinically significant indicators to the benefits of such program and given an increased samples size, we would expect these intervals to be narrower and more precise.

Two assumptions are required to be satisfied in the conduct of network meta-analysis. The transitivity assumption posits that that there are no systematic differences between the available comparisons in this case (rapid hospital, rapid location and conventional

HIV testing) other than the treatments being compared. In our study, we contend that there are fundamentally no differences between all three options other than the location of the testing. Additionally, the risk profile of population studied were known to be increased for HIV due to a number of characteristics including residence in a high HIV prevalence area, clients of an STD and sexual health clinics, and needle exchange programs. Therefore, an argument could be made that there were no systematic differences between the available comparisons. The consistency assumptions were also met in our analysis given the agreement between direct and indirect testing effect estimates that show improved outcomes with rapid testing approaches.

A major limitation of this review is the limited availability of data. The protocol required a fourth testing option, rapid mobile testing however we did not identify any studies that considered this option. We also were only able to identify five studies that met our inclusion criteria. These studies were done within populations that were predominantly high risk thus the findings from this review may not be generalizable to the general population. The studies were also conducted in countries considered high income thus its applicability to lower income countries is also limited.

Finally, there were no studies that measured the long-term impact of rapid HIV testing on HIV treatment, treatment response and long-term viral suppression.

Appendix A: PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving A Network Meta-Analysis

Section/Topic	Item #	Checklist Item	Page reported
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	23
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	25
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	29
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	29
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	30
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	30-31
Information sources	7	Describe all information sources (e.g., databases with dates of	30

		coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	30
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	30-31
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	30
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	31
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	NA
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	32
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	34
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	32
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:	34

		• Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	34
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	35
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	35
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	38
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	39
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	40
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	40-43
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	40-43
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	39
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	

DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	44-47
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	48
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	48
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	NA

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

CHAPTER THREE

Rapid HIV Testing Options Versus Conventional HIV Testing: A Systematic Review of Economic Evaluations.

Abstract

Introduction:

This study reviewed the economic evidence of rapid HIV testing versus conventional HIV testing; evaluated the methodological quality of the economic evaluations of HIV testing studies; and made recommendations on future directions for economic evaluation of HIV testing approaches.

Methods: A systematic review of the literature was conducted following PRISMA guidelines. Various electronic databases for English language economic evaluations of the economic impact of HIV testing studies were searched. We reviewed the study characteristics and methodological quality using standardized tools. We adjusted all costs to 2018 U.S dollars.

Results: Five economic evaluations met the eligibility criteria but varied in the use of comparators, evaluation type, perspective and design. The methodologic quality of the included studies ranged from medium to high. Evidence to support the cost-effectiveness of rapid HIV testing approaches was found. Rapid HIV testing option was associated with cost per quality adjusted life year (QALY) gained ranging from $42,768 to $90,498. Additionally, regardless of HIV prevalence, rapid HIV testing approaches were found to be the most cost-effective option.

Conclusions: There is evidence for the cost-effectiveness of rapid HIV testing including the use of saliva-based testing compared to usual care or hospital-based serum testing. The quality of the included economic evaluations of HIV testing ranged from moderate

to high. Further studies are needed to draw evidence on the relative cost effectiveness for the distinct options of rapid HIV testing.

Keywords: HIV testing; Economic evaluation; High-income countries

Introduction

Human immunodeficiency virus (HIV) infection is a major contributor to the global burden of disease and a leading cause of death (2). With the advent of antiretrovirals and treatment regimens, the disease can now be well managed. As a result, HIV patients now have an improved quality of life and comparable life expectancies with persons uninfected with HIV (53). The process of achieving this improved quality of life can be represented by the internationally recognized framework known as the cascade or continuum of care (53,54). This framework begins with diagnosis of the disease through HIV testing, linkage to care, retention in treatment program, maintenance of treatment adherence and finally sustained viral suppression (44,55).

The importance of testing and early diagnosis is well documented and evidence shows that early treatment improves outcomes significantly for infected individuals and the communities they live (56,57). This premise forms the foundation for the highly effective "*treatment as prevention"* approach (53,58). Getting people aware of their HIV status has been the focus of HIV control agencies. However, recent UNAIDS data shows that about 50% of people living with HIV are unaware of their diagnosis; for example, Canada, France, Spain and the United States report a substantial proportion of undiagnosed HIV cases (6,8,59–61). Rates of undiagnosed HIV tends to be higher among men who have sex with men, youth and minority population groups (61).

Currently, there are numerous HIV testing approaches including serum and saliva-based screening tests (16,62–66). Serum-based testing can be categorized based on the duration to receipt of the test result. In conventional HIV testing, the serum-based

results are usually available within a week; this may require the client to return to the facility to receive the result. For rapid testing approaches, the results are available within 24 hours and do not require clients returning for results notification.

Clinical effectiveness studies of the various HIV testing approaches have been conducted, however economic evaluations of the various approaches from non-American perspectives are lacking. Available economic studies have been conducted in high prevalence low-income African countries (67) and in high prevalence communities in the United States and Europe (68–72). There are individual studies and systematic reviews that considered the effectiveness of rapid HIV testing (16,41,52,73) and cost effectiveness studies of rapid HIV testing options (74), there is no review focused on the economic evidence of rapid HIV testing compared to conventional HIV testing in low-prevalence, high income countries.

This evidence gap is what we seek to address given the potential increase in the access to HIV care and treatment programs starting with HIV testing aimed at achieving the identified United Nations 90-90-90 goals. In particular, the first goal seeks to have 90% of all people living with HIV know their HIV status by 2020 (2). Our literature search of economic evaluation in low prevalence, high income regions showed there was limited evidence available. This systematic review is focused on North America, Australia and Western Europe areas with low HIV prevalence and high incomes with similar HIV epidemiology. These jurisdictions would benefit from economic evaluation of HIV testing to make informed decision about cost effective HIV screening programming and judicious use of health care resources.

The goals of this systematic review are to: (i) search, select, appraise and synthesize published economic evaluations of HIV testing options; (ii) evaluate the methodological quality of the economic evaluations of HIV testing; and (iii) make recommendations regarding future directions for economic evaluation of HIV testing approaches. In addition, this review focuses on the strength and quality of evidence addressing the cost-effectiveness of rapid HIV testing approaches versus conventional testing approaches in the management of HIV infection.

Methods

This work is a systematic review of available literature on the economic evaluations of any rapid HIV testing approach versus conventional serum-based HIV testing. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in the reporting of this article (75).

Search strategy/process

A search of the medical literature was conducted in Medline (indexed, in-process and other non-indexed from 1990 to present), Embase, NHS EED and Tufts Cost effectiveness analysis (CEA) registry to retrieve all relevant literature based on the NHS EED recommended search strategy. Text words used in the search includes ‘economic evaluation’, ‘cost’, ‘cost-effectiveness’, ‘cost-benefit’ or ‘cost-utility’, ‘rapid HIV testing, and ‘HIV testing’. Owing to the language competency/expertise and resources of the review team, the literature search was limited to studies written in English language,

conducted between January 1, 2001 and January 30, 2019 in North America, Australia or Western Europe. This was also supplemented with hand searches.

Inclusion criteria:

For this review, the inclusion criteria were as follows: an economic evaluation study design that was either an economic evaluation, a clinical trial or model-based evaluation conducted in North America, Australia or Western Europe, involving adult patients aged 16 years and older tested for HIV using at least two of the following four HIV testing approaches: (i) whole blood/serum-based hospital-based testing (also referred to as conventional HIV testing approaches); (ii) rapid hospital-based testing; (iii) rapid location-based testing; and (iv) rapid mobile testing.

This review excluded saliva-based testing due to concerns about test performance. Specifically, saliva based testing options were associated with lower specificity when self administered compared to health care provider administered test (10,33).

HIV testing is considered a rapid test if it has the following three components: (i) voluntary enrolment, (ii) rapid testing with results available within 24 hours and (iii) provision of counselling at delivery of results and treatment options.

The economic evaluations considered in this review included cost-effectiveness, cost-utility or cost-benefit analysis. These would include any of the following outcomes: (i) cost per quality adjusted life years (QALY); (ii) cost per HIV test; (iii) cost per HIV transmission prevented; or (iv) total cost of HIV testing program. Studies were excluded if they considered only one testing approach with no comparator. Cost-minimization

analysis and budget impact analysis were excluded from this review. Cost minimization studies were excluded because these are not formal economic evaluations and usually are costing exercises where there is no difference in the effect of the comparators (76–78)

Finally, due to the difference in HIV epidemiology and characteristics of the health care systems, economic evaluations from the Africa, Eastern Europe and Asia were excluded from this review.

Data abstraction

Two independent reviewers (OM and AL) selected eligible publications initially based on titles and abstracts. Potentially relevant articles were abstracted using standardized data abstraction form. This form was also used for data synthesis. Disagreement between reviewers was resolved by a third reviewer (DC).

The following descriptive data were collected for each economic evaluation: study objectives, perspective taken, analysis type and study design, sample size and population studied. Other considerations include comparator(s), intervention, results, and conclusions. All costs have been adjusted to reflect 2018 United States dollars using international exchange rates and the United States Bureau of Labour Statistics inflation calculator for medical costs (79).

Quality assessment

The methodological quality of HIV testing economic evaluations was assessed using two tools: the Drummond’s ten point criteria for economic evaluations and the 24-item

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (80–82) For both checklists, each item was scored as 'Yes' (met the quality criterion), or scored as 'No' (did not meet the quality criterion), or 'Can't tell' where there was insufficient evidence to make a decision. Using the Drummond criteria each 'Yes' was weighted as 10 percent, and this was tallied for each study to arrive at an aggregate score and for the CHEERS criteria, the "Yes" responses were weighed against the total number of criteria for a percentage. This approach has been used in a recently published systematic reviews of economic evaluations(83,84).

The two checklists used had slightly different focus but were nonetheless complimentary. While the Drummond checklist assesses the use of appropriate methodology in the conduct of the economic evaluation and evaluates the validity of the results, the CHEERS checklist is focused on issues related to reporting. Using the CHEERS checklist, studies were assessed into three categories: high if they satisfied greater than 75% of the criteria, average (50 - 75%) and poor quality when less than 50% of the criteria was satisfied.

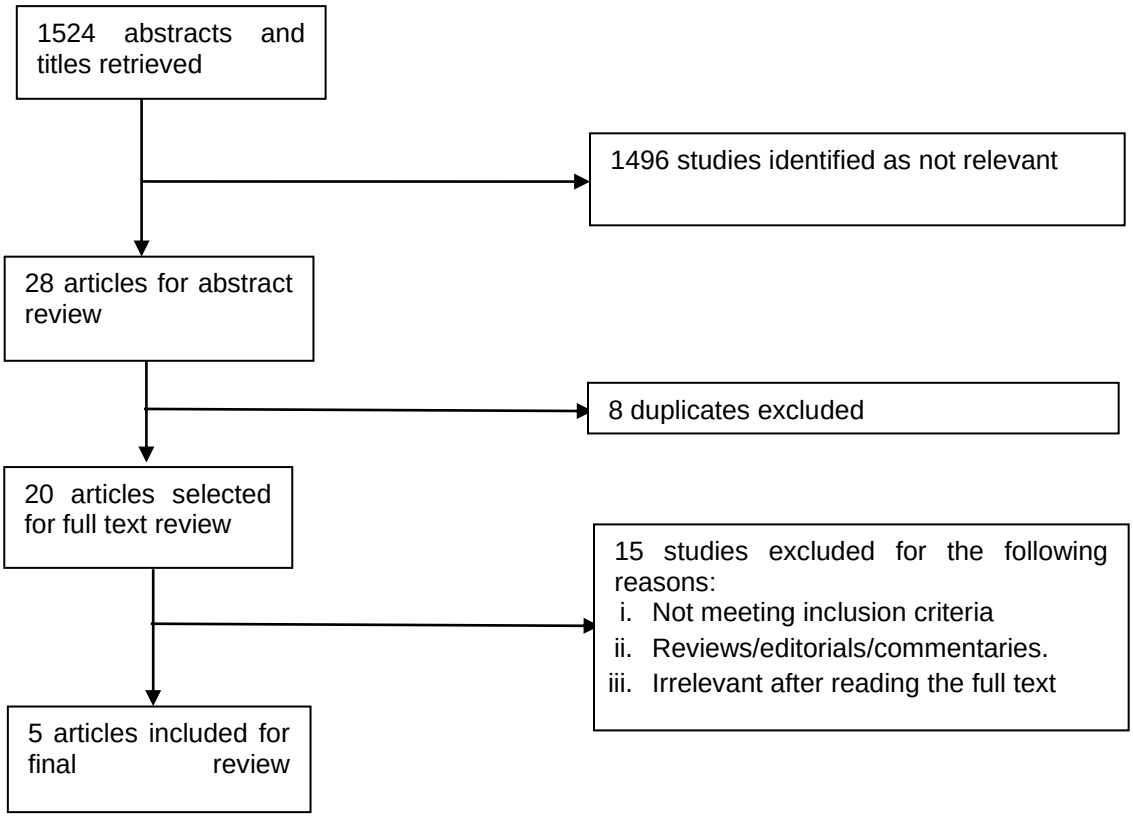
Results

Literature search and screening

The initial search resulted in 1524 records and five were considered for inclusion in this systematic review (See Figure 1). Majority of the studies excluded were due to a lack of comparators in the economic evaluation resulting in the studies being categorized as costing studies. Other reasons for exclusion included studies conducted in jurisdictions

outside of specified geographic location, evaluations of hospitals or organization-specific testing programs that were not explicitly evaluations of HIV testing approaches.

Figure 8: PRISMA Flow Diagram



Study and patient characteristics

Five primary articles met the inclusion criteria and were considered for data analysis and synthesis (85–89). An overview of the study and methodological characteristics, study populations, interventions and outcomes of the five economic evaluations included in the review are provided in Table 5. The earliest economic evaluations in this review were published in 2005 (87,89), and the remaining three published between 2010 and 2012 (85,86,88). All the included studies in this review were conducted in the United States. Majority of the publications (50%) evaluated costs from the perspective of the society (85,86,89,90).

All the included studies were model-based economic evaluations. The evaluations included were two cost-effectiveness studies (86,88) and three cost-utility studies (85,89,90).

One study (35) was conducted from the perspective of the healthcare insurer and the remaining four (85,86,89,90) were from a societal perspective. Four studies (86,88–90) considered a lifetime horizon in the evaluation, and one study (32) considered a 20-year time horizon.

All studies included populations considered at high risk for HIV (prevalence greater than 1%) such as injection drug users, populations from inner city US populations as well as members of the general population with assumed prevalence greater that 1% while the general population prevalence was approximately 0.1% (85–88,90).

Comparative interventions

Comparisons considered in the included studies include one-time and repeat interval rapid screening, rapid emergency department (ED) testing versus usual care, various rapid testing approaches (85–87,91). These approaches while varied have the common theme of a rapid HIV testing arm that was either compared to the usual standard of care or other rapid HIV testing approaches.

All five studies reported outcomes as cost per quality adjusted life years and found that rapid HIV testing approaches were cost-effective. Sanders et al, 2010 found nurse-initiated routine screening with rapid HIV testing and streamlined counseling was more cost-effective at $42,769/QALY while Dowdy et al, 2011 found targeted HIV screening

in emergency departments cost effective at $90,498.34 per QALY. Furthermore, this option at a willingness to pay threshold of $100,000 per QALY gained, was cost-effective in 89% of simulated scenarios (86,88).

The comparisons considered in the included studies include one-time and repeat interval rapid screening(85), and various rapid testing approaches including oral testing (86,88,89).

When varying prevalence of HIV was considered, rapid HIV screening was found to range in cost-effectiveness from $50,429/QALY in settings with at least 1% HIV prevalence to $91,171/QALY in settings with 0.1% HIV prevalence (90). Another study by Paltiel et al, 2005 found that among high risk populations, one-time screening costs $51,284/QALY. The study further found that testing every five years cost $71,227/QALY and by reducing the frequency of testing to every three years, it cost $89,746/QALY (89).

Study quality assessment

Table 6 presents the distribution of scores across each of the 10-item Drummond checklist according to whether or not each study fulfilled the criterion (or was not applicable) in terms of study design, execution and reporting of relevant information on the nature and methods used in the study (92). We used a similar approach as previous authors where criteria met on the checklist is presented as a percentage (83,84,93). Across included studies, we noticed high variability in methodological quality. The scores presented as percentages of criteria met ranged from 50% to 90%. One study

(85) met nine criteria out of the 10 domains scoring 90%, two studies (86,88) scored between 70 - 80% and the remaining two studies scored 50% or less (89,90).

Specific concerns on the Drummond checklist showed that most studies did not accurately measure the costs and consequences or justify that the valuation costs and consequences were credible (See Table 6).

Additionally, the quality evaluation of the included studies based on the CHEERS checklist is summarized in Table 7. Using the CHEERS criteria, all included studies were assessed as high quality.

While most criteria were adequately reported, there were some criteria that were generally underreported. The abstract usually did not have enough information about base case and the uncertainty associated with the outcome. We also identify that none of the studies adequately reported the populations and methods used to elicit outcome preferences. There were also concerns about how the studies reported the analytic methods used in the evaluations.

All included studies (85,86,88–90) performed a sensitivity analysis and provided varying depths of reporting about the sensitivity designs used (Table 8).

Table 8 shows the modelling approaches used by the various evaluations included in the analysis. One study (33) was a decision analysis model, three studies (88–90) were transition simulation models and the last evaluation was conducted using a dynamic compartmental model (85). Two (89,90) of the transition model evaluations used a four

state transitions using Cost-Effectiveness of Preventing AIDS Complications (CEPAC) data (94). The last model-based study used a seven state model (88)).

Discussion

Economic analysis is imperative to assist with rational decision making about the allocation of limited health resources. It seeks to provide information about the value of competing health interventions. Our review identified five studies that reported economic evaluations of rapid HIV testing approaches in North America. While our inclusion criteria expanded to studies conducted in Western Europe and Australia, we were unable to find any such evaluations from these countries. For this review, we have adjusted all cost figures to 2018 United States dollars. Included economic evaluations reported a wide variation in the use of comparators, evaluation type, perspective and design, thus statistical pooling of the estimates was not feasible.

The studies included in this analysis show that the use of rapid HIV testing approaches including the use of saliva-based screening tests may be a cost-effective option compared to usual care or hospital-based serum testing options. The conclusion that can be drawn from the highest methodological quality studies (studies that scored 80% or higher on the Drummond checklist) showed that rapid testing approaches was cost effective compared to conventional hospital-based serum HIV testing with an ICER between $36,081 per QALY and $39,376 per QALY (85).

Lower quality studies also showed that rapid HIV testing approaches was cost effective at an estimated $51,284 per QALY. However we found an increase in the cost per

QALY when the test was used in populations with lower prevalence of HIV increasing to about $91,171 per QALY (89). Our study considered economic evaluations from high income countries in North America, Europe and Australia where the pattern of disease is similar. We did not find studies from any country other than the United States therefore the estimates provided reflect more of the American health care system. While these ICERs are for the most in excess of the $50,000 per QALY threshold, they are below the higher limits of $100,000 threshold considered acceptable in some higher income countries (95–100).

These higher ICER thresholds may potentially reflect an overestimation of the ICER's because of the nature of the healthcare system that has shown a trend towards a willingness to pay threshold of US$ 150,000 per QALY gained (101). These ICER values would be considered acceptable in most of the target countries and jurisdictions. In Canada for example, the ICER values would be considered acceptable because they are generally below the maximum of the commonly used Canadian threshold of between $20,000 - $100,000 per QALY gained and in some circumstances when considering high prevalence populations is lower than $50,000 per QALY gained (77,96). While Australia and United Kingdom do not have a fixed threshold value for ICER given the recommended ICER thresholds, some of the ICER amounts would be considered not acceptable (95,100).

Two of our included studies (90,102) used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model (94), a mathematical simulation of the detection, natural history and treatment of HIV disease in the US and it is thus expected that the findings

would be consistent. It is also noted that with variations in the settings and populations of interest, rapid HIV testing approaches remained cost-effective when compared to conventional approaches.

Most of the studies considered the use of rapid HIV testing as an approach resulting in early detection of disease with subsequent connection to care and treatment shown to result in improved outcomes as well as contributing to prevention of new cases of HIV. The outcome measures included cost per QALY gained, cost per HIV test and cost per test notification. These outcomes are important because the benefits of early HIV diagnosis extend beyond potential immediate improvements to individual client health outcomes and include other considerations such as prevention of new HIV transmission. These outcomes are however not adequately reported.

Finally, it is important to highlight that none of the included studies explicitly considered equity factors including place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital (103). This is likely because included studies considered the traditional approach of economic evaluation that ‘a QALY is a QALY’ and all outcomes should be weighted equally, regardless of the characteristics of people receiving (76). There is, however, a school of thought that considers this a value judgment that is questionable when applied to public health. The suggestion is for equity considerations to be incorporated in economic evaluations in public health (104–106).

Limitations

While this study is to our knowledge the first systematic review of economic evaluations of HIV testing approaches, we identified a few limitations. First is the limited number of studies available for inclusion in the review. Second, we were unable to find any studies from other high-income economies that have similar HIV prevalence, thus generalizing to these high-income countries may be difficult. Also, this review did not include studies published in other languages other than English.

None of the studies considered the cost of rapid HIV testing per new HIV transmission prevented; an outcome that would be significant in advancing an economic argument for the use of rapid HIV testing approaches as an integral population strategy in HIV programming.

The Consumer Price Index (CPI) used to adjust the costs is an indicator of changes in consumer prices experienced by populations. It is obtained by comparing over time, the cost of a fixed basket of goods and services purchased by consumers (107–109). This approach is limited because it does not account for other options that may not be included in the fixed basket used in the assessment and likely ignores the cost savings from use of less costly alternatives (109).

We also identify that the Drummond checklist while appropriate for assessing study inclusion criteria may not adequately address contextual and health system factors related to rapid HIV testing. Also, we found that none of the five articles met Drummond's entire 10-item checklist (Table 6) thus leaving a few high-quality economic evaluations. Additional limitations of the checklists were the lack of a developed scoring

algorithm. Hence using the Drummond and CHEERS criteria each 'Yes' response was weighted against the total number of criteria for an aggregate score.

The articles included in this review were published between 2005 and 2012 with none published since the recent changes made in HIV clinical management such as the 90-90-90 strategy which requires a scaling up of HIV testing and treatment and aims to have 90% of person HIV infected tested and aware of their status, 90% of infected persons on antiretroviral treatment and viral suppression in 90% of persons on antiretroviral drugs (2). Finally, we cannot exclude publication bias as almost all the economic evaluations demonstrated the cost-effectiveness of rapid HIV testing.

Conclusion

In conclusion, evidence exists from the United States that supports the use of rapid HIV testing approaches compared to conventional HIV testing approaches. The evidence from this review is from a single low HIV prevalence high income country and does not account for the difference in healthcare system characteristics making it difficult to generalize to other high-income low HIV prevalence countries. The costs and outcomes associated with rapid HIV testing approaches suggest that it is a cost-effective approach for population HIV screening particularly among higher prevalence communities. However, there is inconsistent evidence of the use of rapid HIV testing approaches in lower prevalence settings. It would be of significant benefit to obtain estimates from other countries jurisdictions besides the United States to account for the differences in healthcare system characteristics and enable generalization to these settings.

Table 5: Overview of the five economic evaluations reviewed by study characteristics and outcomes with all costs in 2018 US

Authors	Country	Setting	Perspective	Analysis type	Study design (follow up)	Time horizon	Population	Interventions	Outcomes
Cipriano LE et al, 2012	United States	US Urban center	Societal	Cost-utility	Deterministic dynamic compartmental model	20 years	IDU's and non-IDU's in opioid replacement therapy	One-time and repeat interval screening	ICER; Costs per life year; $36,081 per QALY versus one-time screening
Sanders GD et al, 2010	United States	US	Perfect insurer(110)	Cost-effectiveness	Trial based Markov model	Lifetime	Emergency department	Model A: traditional HIV counseling and testing; Model B: nurse-initiated routine screening with traditional HIV testing and counseling; Model C: nurse-initiated routine screening with rapid HIV testing and streamlined counseling	Cost per QALY vs Model A: Model B: Extended dominance Model C: $ 42,769 /QALY; Cost per life year (LY) vs Model A Model B: Extended dominance Model C: $ 31,392.35 /LY
Dowdy DW et al, 2011	United States	Emergency departments	Societal	Cost-effectiveness	Decision analysis	Lifetime	Persons at higher risk of HIV	Targeted ED HIV screening versus clinic-based	$ 96,727.44 for targeted screening program; $ 53.51 per screening

								approaches	test; $ 90,498.34 /QALY for targeted HIV screening versus clinic-based approaches
Paltiel A D et al, 2005	United States	USA	Societal	Cost-utility	Model-based evaluation: Monte Carlo, state-transition framework	Lifetime	High risk, CDC threshold and US general cohort	Routine voluntary HIVCTR; Testing at presentation with opportunistic infections	High risk population: One-time ELISA versus current practice: $ 51,283.93 /QALY, More frequent screening >$50,000/QALY In the general population: all screening regiments are >$50,000/QALY
Walensky R P et al, 2005	United States	Hypothetical cohort of 100 million US inpatients	Societal	Cost-utility	State-transition simulation model	Lifetime	Hypothetical cohort of 100 million US inpatients	HIV screening based on HIV prevalence	Screening versus no screening, $ 50,429.20 /QALY in settings with 1% HIV prevalence; $ 91,171.44 in settings with 0.1% HIV prevalence

Table 6: Summary of Drummond evaluation of methodological quality

Drummond criteria	Cipriano LE et al, 2012	Sanders GD et al, 2010	Dowdy DW et al, 2011	Paltiel AD et al, 2005	Walensky RP et al, 2005
Well-defined question?	Yes	Yes	Yes	Can't tell	Can't tell
Adequate description of comparators?	Yes	Yes	Can't tell	Can't tell	Can't tell
Evidence of effectiveness?	Yes	Yes	Yes	Yes	Yes
Relevant costs/consequences?	Yes	Yes	Yes	Can't tell	Can't tell
Costs/consequences accurately measured?	No	No	Can't tell	Can't tell	Can't tell
Were the valuation costs/consequences credible?	Yes	Can't tell	Can't tell	Can't tell	Can't tell
Was discounting used as appropriate?	Yes	Yes	Yes	Yes	Yes
Were incremental analyses appropriately reported?	Yes	Yes	Yes	Yes	Yes
Were sensitivity analyses reported?	Yes	Yes	Yes	Yes	Yes

Was the discussion adequate?	Yes	Yes	Yes	Yes	Yes
Percent of criteria met	90%	80%	70%	50%	50%

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Score
Cipriano LE et al, 2012	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	79%
Sanders GD et al, 2010	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	83%
Dowdy DW et al, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	88%
Paltiel AD et al, 2005	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	83%

Table 7: Quality of the included studies based on the CHEERS checklist

Walensky R P et al, 2005	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	88%
Completed criteria	100 %	20 %	100 %	100 %	100 %	100 %	100 %	100 %	100 %	80 %	80 %	0%	80 %	100 %	100 %	80 %	40 %	60 %	100 %	80 %	100 %	100 %	100 %	100 %	

Table 8: Sensitivity analysis descriptions

Authors	Analysis type	Study design (follow up)	Modelling method	Type of sensitivity analysis	Parameters
Cipriano LE et al, 2012	Cost-utility	Deterministic dynamic compartmental model	Dynamic compartmental model	Univariate deterministic sensitivity analysis	No of IDU's by city; Prevalence of HIV and HCV
Sanders GD et al, 2010	Cost-effectiveness	Trial based Markov model	Markov model	Univariate and multivariate deterministic sensitivity analysis; Probabilistic sensitivity analysis	HIV test characteristics; Test probability; Probability of undiagnosed HIV; Probabilities of receiving HIV test result given positive and negative result
Dowdy DW et al, 2011	Cost-effectiveness	Decision analysis	Decision analysis	Univariate deterministic sensitivity analysis	Prevalence of undiagnosed HIV; Annual HIV transmission rate; Lifetime cost of treating new HIV cases; Monthly test volume; HIV awareness
Paltiel A D et al, 2005	Cost-utility	Model-based evaluation: Monte Carlo, state-transition framework	State-transition simulation model	Multivariate deterministic sensitivity analysis	Testing frequency; Proportion of persons returning for results; Efficacy of antiretroviral (ARV); Proportion of infected on ARV
Walensky R P et al, 2005	Cost-effectiveness; Cost-utility	State-transition simulation model	State-transition simulation model	Univariate deterministic sensitivity analysis	Testing costs; CD4 counts; HIV Prevalence; Cost of ARV

CHAPTER FOUR

Economic Evaluation of HIV Testing - A Discrete Event Simulation

Title: Economic Evaluation of HIV Testing - A Discrete Event Simulation

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Type of article: Cost utility analysis

Abstract

Introduction: Undiagnosed HIV infected persons continue to transmit the virus and thus represent a significant public health challenge. Ongoing efforts are aimed at addressing this challenge including increased HIV testing and the use of rapid testing approaches. While there is evidence of program effectiveness of the use of rapid approaches, evidence of economic effectiveness is limited.

Objectives: To estimate the clinical and economic benefits of the use of serum based rapid HIV testing approaches as a population programming tool in low prevalence high income countries.

Methods: We developed a HIV progression model based on a modified the CDC disease staging and used a discrete event simulation modelling approach to simulate the progress of HIV infected persons diagnosed using the various testing approaches. This economic evaluation was conducted using a health system perspective.

Results: In our reference case analysis modelling the progression of HIV from diagnosis to death, the use of conventional HIV testing was the most expensive costly option at $879,019.67 and produced 29.49 QALY's, while the least expensive option was associated with the use of rapid hospital-based HIV testing at $878,977.47 also producing 29.49 QALY's. At a willingness to pay (WTP) threshold of $50,000 rapid hospital-based HIV testing was the most likely cost-effective testing option in 80% of replications and this continued at higher WTP thresholds.

Conclusions: We found that rapid hospital-based HIV testing is more cost-effective than convention serum testing. This was true for individuals at increased risk for HIV living in high-income, low HIV prevalence countries.

Introduction

Undiagnosed HIV infected persons in the community represents a significant public health challenge because with increased proportions of undiagnosed, there exists a higher level of risk for continued HIV transmission (16–18). When HIV infected persons are diagnosed and enrolled in the cascade of care, they are commenced on antiretroviral therapy (ART) early in the disease process and this results in significantly reduced transmission risk to uninfected partners. It has also been found that there is a lower morbidity and mortality rates compared to those in whom diagnosis and treatment is delayed (21–23).

Recognizing the risks due to undiagnosed HIV cases, the Joint United Nations Programme on HIV/AIDS (UNAIDS) developed the “Getting to Zero” strategy and the 90-90-90 strategy (2,24,111). The strategy is based on three major areas namely: revolutionizing HIV prevention; catalysing the next phase of treatment; and advancing human rights and gender equality for the HIV response. The first of these areas focuses on “*fostering political incentives for commitment and catalysing transformative social movements regarding sexuality, drug use and HIV education for all, led by people living with HIV and affected communities, women and young people*”. Additional consideration was also given to ensuring equitable access to cost-effective HIV prevention programmes (24). The 90-90-90 strategy aims to achieve the following targets: diagnose 90% of all HIV-positive persons; provide antiretroviral therapy (ART) for 90% of those diagnosed; and achieve viral suppression for 90% of those treated by 2020.

The starting point for both strategies is early diagnosis that has been associated with improved outcomes for patients and as part of the 90-90-90 strategy, the first component is ensuring over 90% of people with HIV to know their status (2). Achieving this is only through increased HIV testing and different studies have demonstrated that the use of other testing options different from the conventional hospital based testing approaches results in improved uptake of testing and an increased proportion of tests (16,112,113).

There are various forms of HIV testing approaches, the most common form is hospital blood-based testing commonly referred to as conventional HIV testing. There are other alternatives based on a mix of location and sample types used in the testing. These sample used in rapid testing include saliva samples and pin-prick blood drop samples. The non-hospital-based approaches have allowed for testing to be conducted in a variety of locations such as homes, workplaces, parole offices, social meeting places as well as other community settings. There have also been the adoption of mobile testing approaches that further seeks to improve access to testing and by extension meeting the stated goal of the various strategies (16,26–28).

These studies have found that rapid testing approaches are more effective however they have not been able to provide estimates of the economic effectiveness of what type of rapid testing provides the best value for money and this is what this economic evaluation seeks to provide (16,26–28).

Methods

This economic evaluation is conducted from the Canadian health system perspective. While a societal perspective is sometimes advocated in economic evaluations, the goal of the analysis is to facilitate a decision by a publicly funded ministry of health in Canada. Given the assumed objective of the ministry of maximising the health of the population covered then it is necessary to focus on the direct costs associated with HIV testing and clinical management to the health care system as inclusion of costs outside of the perspective would not be consistent with the underlying objective of the system – i.e. it would suggest the willingness to trade health benefits for other benefits in other sectors (76).

The analysis employed a discrete event simulation (DES) cost-effectiveness model developed in Microsoft Excel to describe clinical progression of HIV patients diagnosed using different testing approaches over time. Using DES allows for modelling of the various patient populations that exists and accounting for the events (change in disease stages) that can happen differently between various patients.

Discrete event simulation assumes that there is no change in patient status “event” between events therefore simulation is only concerned with the next event. The choice of discrete event simulation as the primary modelling approach for this study is justified because it is considered the optimal approach when dealing with complicated diseases which is difficult to define by discrete health states and that require modelling over long time horizons (114–116).

The model compared three different HIV testing approaches in a Canadian population: The testing options include whole blood/serum-based hospital-based testing (also referred to as conventional HIV testing approaches); rapid hospital-based testing; and rapid location-based testing. Our simulation model assesses the costs that are associated with HIV care following diagnosis using each of these approaches.

The disease model is based on the progression of a HIV infected person through the various stages (events) using a modified Center for Diseases Control staging. See Figure 9.

The results are presented as cost per person tested, and cost per quality adjusted life years (QALY) gained. As recommended by the updated CADTH guidelines, the reference case analysis will be conducted using a probabilistic analysis by assigning probability distribution to input parameters and randomly selecting values for each parameter from their distribution. This allows assessment of the impact of uncertainty around the input data estimates (76).

Cost effectiveness of the various testing approaches is captured by estimating clinical response to treatment based on HIV disease progression using a modified Centers for Disease Control staging. Effectiveness data of the various testing approaches in connecting HIV infected persons to care and treatment programs were taken from the first manuscript of this thesis which is systematic review and network meta-analysis (NMA).

Figure 9: Simplified schematic of the simulation model for HIV disease progression.

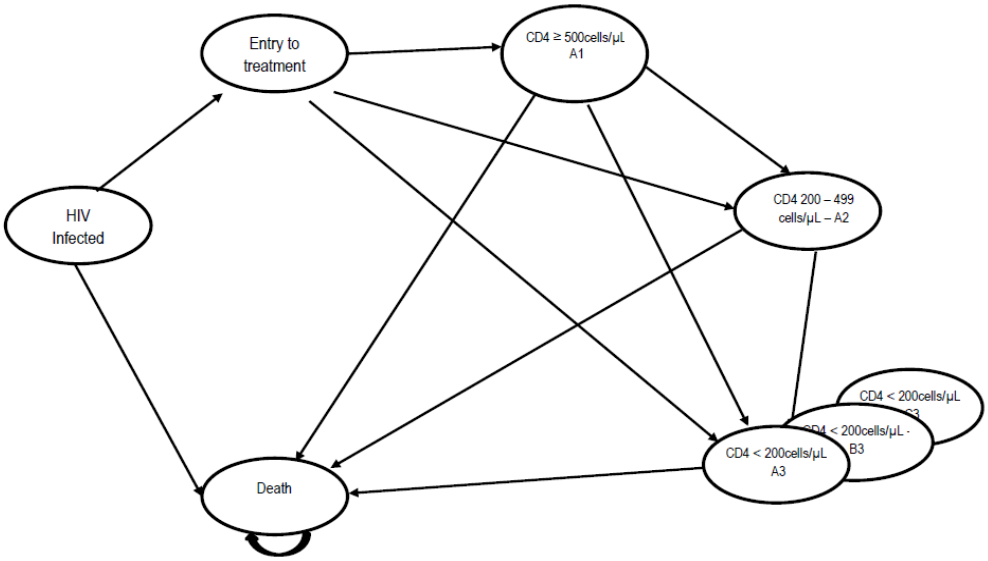


Table 9; Data sources and model inputs

Description of variable	Value	Probability distribution	References
Utility Values			
CDC Stage A1	0.798	Normal (0.798, 0.003)	(117)
CDC Stage A2	0.784	Normal (0.784, 0.004)	(117)
CDC Stage A3	0.778	Normal (0.778, 0.003)	(117)
CDC Stage B3	0.750	Normal (0.75, 0.005)	(117)
CDC Stage C3	0.742	Normal (0.742, 0.007)	(117)
Death	0		
Baseline mortality rates			
Mortality - A1 (Alpha, Beta)	0.0025	Beta (146, 69496)	(118)
Mortality - A2 (Alpha, Beta)	0.0034	Beta (170, 49657)	(118)
Mortality - A3 (Alpha, Beta)	0.0034	Beta (170, 49657)	(118)
Mortality - B3 (Alpha, Beta)	0.0057	Beta (280, 48935)	(118)
Mortality - C3 (Alpha, Beta)	0.0283	Beta (977, 34574)	(118)
Discount Rate	0.015		(76)
Relative risk of entry into treatment programs vs conventional HIV testing			
Hospital based rapid HIV testing (LogMean. Standard error)	2.52	Log normal (0.22, 0.91)	(119)
Location based rapid HIV testing (LogMean. Standard error)	1.76	Log normal (0.60, 0.90)	(119)
Probability of entry into treatment program: Conventional HIV testing	0.90	Log normal (-0.21, -0.01)	(2)
Number of tests per annum with rapid approaches	1.63	(1.49, 1.79	(41)
Number of tests per annum with conventional testing	1.42	(1.29, 1.57)	(41)
Resources and costs			
Costs associated with testing			
Cost associated with conventional HIV testing	$51.94	Gamma (100, 0.52)	(120) and other cost estimates obtained from HIV clinic staff in Sask. Health Authority
Cost associated with rapid hospital-based testing	$50.63	Gamma (100, 0.51)	
Cost associated with rapid location-based testing	$48.93	Gamma (100, 0.49)	
Costs associated with clinical management by disease stage			
Costs associated with CDC Stage A1	$21,663.26	Gamma (100, 261.63)	(121)
Costs associated with CDC Stage A2	$24,598.46	Gamma (100, 245.98)	(121)
Costs associated with CDC Stage A3	$27,533.66	Gamma (100, 275.34)	(121)
Costs associated with CDC Stage B3	$32,983.11	Gamma (100, 329.83)	(121)
Costs associated with CDC Stage C3	$40,298.11	Gamma (100, 402.98)	(121)

Data inputs for this analysis were obtained from different sources. The utility values associated with the different HIV stages were obtained from the study by Kauf et al (117). For the transition and mortality probabilities associated with the various disease stages, we were unable to identify data that provided these estimates using the modified CDC staging, we therefore used transition probabilities from a Canadian study that used the CD4 based staging approach (118). (Table 9). The CD4 count based classification used in the Canadian study closely aligns with the modified CDC staging that used but CD4 cell counts and clinical presentation. The life expectancy for patients in this model was capped at 60 years of age consistent with the findings from a 2015 study using the Canadian Observational Cohort (CANOC) collaboration (122).

For effect estimates for entry into care and treatment programs, among persons who were diagnosed using conventional hospital based tests, we estimated that 90% of HIV infected persons who are aware of their status were enrolled in treatment programs. This was used as a baseline and the estimates from the first manuscript a network meta-analysis was weighted against these effect measures to determine the probability of entry into treatment programs (119).

Read et al, 2013 (41) estimates the average number of HIV tests per individual per annum. This estimate was applied to both conventional HIV testing and rapid HIV testing options. Using the derived value for probability of entry into treatment programs and the number of tests, we determined the rate of entry into treatment program by calculating the natural logarithm of 1 minus the probability of entry into treatment programs multiplied by the number of HIV tests expected per person per year.

The associated costs of HIV testing and care and treatment estimates were obtained from a combination of sources including published literature and consulting with content experts (121,123,124). See Table 9. The various costs were all adjusted using the Bank of Canada inflation calculator to 2018 Canadian dollars (125). Costs and outcomes are discounted to present values at a rate of 1.5% per year per Canadian Agency for Drugs and Technologies in Health guidelines (76).

Table 10: Derived data

Description of variable	**Value**
Probability of disease progression	
Conventional HIV testing	0.049
Hospital based rapid HIV testing	0.118
Location based rapid HIV testing	0.084
Mobile rapid HIV testing	0.079
Probability of mortality by disease stage	
Probability of mortality associated with CDC stage A1	0.049
Probability of mortality associated with CDC stage A2	0.095
Probability of mortality associated with CDC stage A3	0.330
Probability of mortality associated with CDC stage B3	0.405
Probability of mortality associated with CDC stage C3	0.483

Results

Reference Case Analysis

Our reference case was consistent with the updated Canadian Agency for Drug Technologies and Health (CADTH) guidelines (76). The reference case was an adult between 18 - 60 years of age at risk for HIV in a high-income country. We found that

modelling the progression of HIV from diagnosis to death, the use of conventional HIV testing was the most expensive option at $879,019.67 and produced 29.49 QALY's, while the least expensive option was associated with the use of rapid hospital-based HIV testing at $878,977.47 producing 29.49 QALY's.

Table 11: Results for reference case

Testing approaches	***QALY gained***	***Costs***	***Sequential analysis***
Non dominated strategies			
Conventional testing	29.49	$ 879,019.67	
Rapid hospital	29.49	$ 878,977.47	$6,630.99
Dominated strategies			
Rapid hospital	29.49	$ 878,977.47	Subject to extended dominance through rapid hospital-based testing and conventional testing

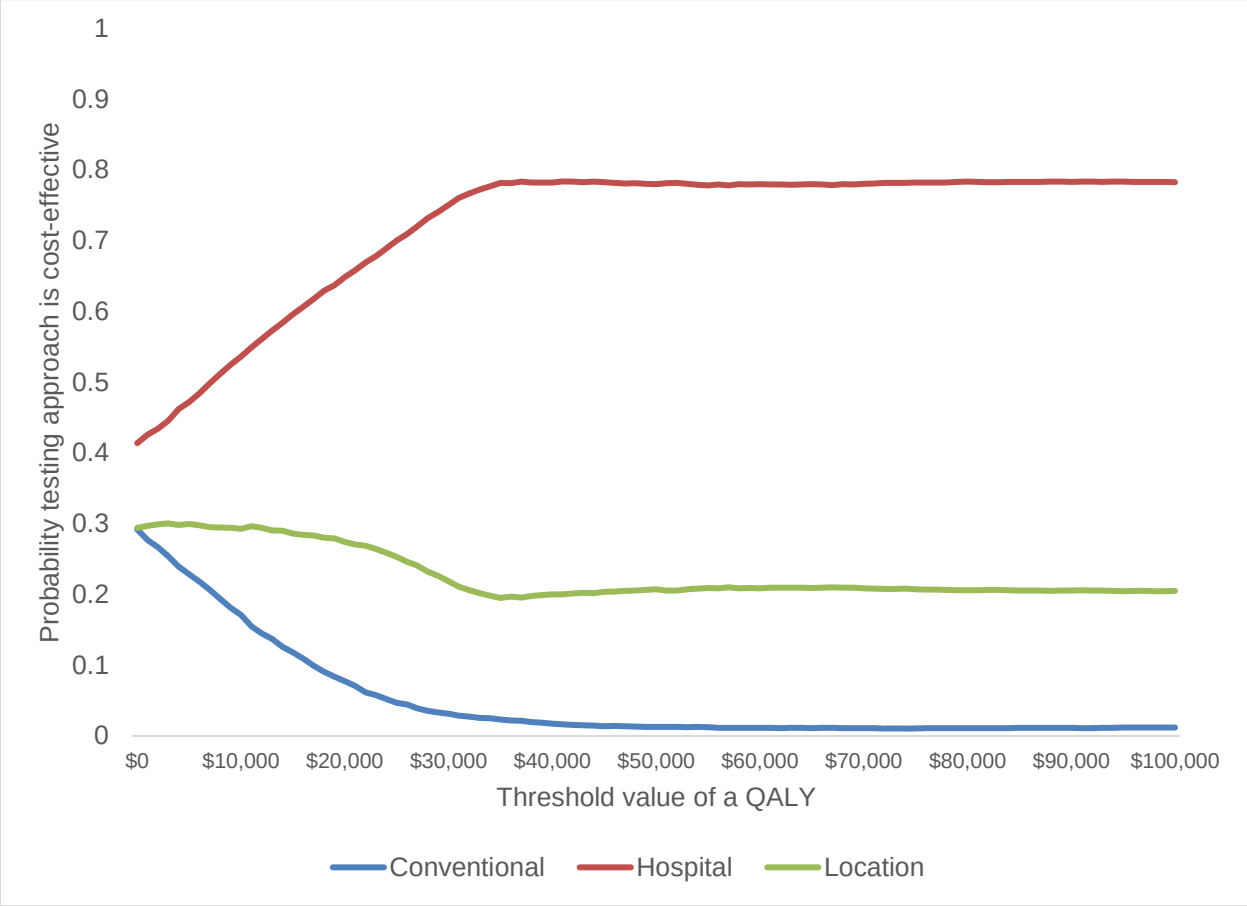
Table 12: Results for one-way sensitivity analysis varying discount factor

Testing approaches	***QALY gained***	***Costs***	***Sequential analysis***
Discounting at 0%			
Conventional testing	44.42	$1,345,962.92	
Rapid hospital	44.42	$1,345,908.93	$5,442.09
Dominated option			
Rapid location	44.42	$1,345,901.60	Subject to extended dominance through rapid hospital-based testing and conventional testing
Discounting at 3%			
Conventional testing	20.93	$614,854.83	
Rapid hospital	20.94	$614,818.05	$6,749.53
Dominated option			
Rapid location	20.94	$614,812.80	Subject to extended dominance through rapid hospital-based testing and conventional testing

The results were consistent when a deterministic analysis was conducted with rapid location-based testing producing more QALY's at a lower cost.

Finally, we summarize the uncertainty around our decision by presenting the results with a cost-effectiveness acceptability curve that shows that over disease course at a WTP threshold of $50,000, rapid hospital-based HIV testing was the most likely cost-effective testing option in 80% of replications and this continued at higher willingness to pay thresholds. See Figure 10.

Figure 10: Cost-effectiveness acceptability curve of rapid HIV testing options - Reference case



Discussion

There continues to be limited resources available for health care programming. As such, funding decisions require consideration of not only the clinical effectiveness of the available options but also what options provide the best value for money. Healthcare systems in general seek to optimize the available resources and this also applies to HIV programming.

In HIV programming, it has been established that early identification of disease and prompt commencement of antiretroviral therapy is associated with improved outcomes both for the individual, reduced viral load and reduced risk of disease transmission. The challenge has always been how best to reach the various subsets of population with high risk for disease. It has been demonstrated in the literature that the use of rapid HIV testing approaches is associated with earlier diagnosis and enrollment in care and treatment programs institution [1,28–31]. However, the cost-effective rapid HIV testing approach has not been conclusively demonstrated in the literature.

Our analysis of the cost-effectiveness of conventional HIV testing versus the other variations of rapid HIV testing stratified by location based and hospital; based testing showed that for an adult at increased risk for HIV in low prevalence country such as Canada, the use of the rapid hospital-based HIV testing was the most cost-effective option and thus represents an effective use of health care funding allocation from a public payer perspective.

Although not stratified by location, previous economic evaluations conducted in similar prevalence settings primarily the United States demonstrate the cost-effectiveness of rapid HIV testing approaches. Sanders et al, 2010 found that nurse-initiated routine screening with rapid HIV testing and streamlined counseling (classified as rapid hospital-based HIV testing) was more cost-effective compared to traditional HIV counselling and testing [32]. Dowdy et al, 2011 report that the use of targeted emergency department (ED) rapid HIV screening versus conventional clinic based approaches was similarly more cost effective and Paltiel et al, 2005 report that a one-

time use of enzyme linked immune-sorbent assay compared to conventional testing among high risk populations cost about $51,300/QALY [33,34].

Our study has several strengths. First, to the best of our knowledge this is the first study that sort to identify the cost-effectiveness of rapid HIV testing approaches stratified by the location where the tests were conducted. As stated previously, other reviews have considered rapid HIV testing approaches as a homogenous group not acknowledging that there may be a differential impact due to location of testing.

Second, this analysis modelled the effect of HIV testing over the life course of an infected individual and this enabled us to estimate the long-term impact of early HIV diagnosis not only in terms of health outcomes and also the associated cost implication.

Third, we used a discrete event simulation approach that is better suited to modelling diseases where patients have different characteristics. It is also an approach that is well suited to working with diseases that have a significant number of subpopulations as with HIV where there are different risk factors that may predispose persons to HIV. The modelling approach is also one that has clinical validity and able to incorporate the clinical history.

Our study is not without its limitations. First, we did not include rapid mobile HIV testing in the economic model as previously planned. We acknowledge that while several care and treatment programs use mobile HIV testing, we were not able to find clinical effectiveness data of connection to care and treatment programs to populate our model and therefore was not included in our model.

Second, an argument may be made that the groupings of rapid HIV testing were too few however we are convinced that this is the best grouping and number possible at this time.

Third, our model estimates of disease progression used the CD4 count classification alone instead of the earlier planned modified CDC classification which had to be revised because of unavailability of clinical data. We are nevertheless convinced that this did not affect the quality of our conclusions.

Our analysis addressed three types on uncertainty common to economic evaluations. We addressed methodological uncertainty by applying the appropriate discount rates to costs and outcomes. For parameter uncertainty, the probability distributions applied ensured that the true value of each model input was represented. To address this, the reference case analysis was conducted consistent with the 2017 CADTH guidelines that recommends probabilistic analysis (76). While CADTH suggests scenario analysis in instances where impact of changes is devoid of uncertainty, we did not conduct scenario analysis because of the fair amount of uncertainty around healthcare associated costs for different disease stages.

Our analysis considered the public payer perspective only and not the societal perspective. This was done because our objective was to inform resource use by the third-party payer and in the Canadian context these are usually provincial and federal governments. We also used the public payer perspective because of the data limitations about variables such as days of work lost, employment insurance payments and other allied health expenses that are not readily available.

In conclusion, we evaluated the cost-effectiveness of three HIV testing approaches namely conventional HIV testing and two rapid HIV testing approaches. We found that from a population-based programming standpoint for individuals at increased risk for HIV living in high-income, low HIV prevalence countries, the more cost-effective testing option is the use of rapid hospital-based HIV testing.

CHAPTER FIVE

Study summary

Introduction

Rapid HIV testing approaches have increasingly become part of the cascade of care for HIV clinical management. Due to its relative ease of use, early results availability and excellent test properties, it has resulted in an increase in the proportion of HIV diagnosis with linkages to care and treatment programs. The expectation is that consistent with the 90-90-90 strategy 90% or persons infected with HIV will be diagnosed, 90% of those infected will be provided with antiretroviral therapy and of these 90% would be virally suppressed (2).

Across various jurisdictions there is consistent evidence for the effectiveness of the use of rapid HIV testing options including both low to middle income, higher prevalence countries and higher income low prevalence countries (16,34,41,43,126). There is also economic evidence supporting the use of these technologies however few studies have attempted to assess the relative effectiveness and cost effectiveness of the different types of rapid HIV testing approaches.

The overall aim of this dissertation was to evaluate the relative effectiveness of rapid HIV testing approaches stratified by test settings and apply the effectiveness estimates derived to conduct an economic evaluation of the use of rapid HIV testing approaches as applicable to a Canadian population characterized as one of low prevalence and higher income.

Summary of research findings

The first manuscript, titled “Rapid HIV Testing for improving uptake of HIV/AIDS services in people with HIV Infection - A Systematic Review and Network Meta-

analysis” was a synthesis of the current literature on the effectiveness of various types rapid HIV testing compared to conventional testing. Also considered was the relative effectiveness between the various rapid testing approaches.

The outcomes considered in this systematic review were patient important ones that were assessed by the authors to have direct impacts on the health outcomes of individual patients as well population level impacts. Some of these outcomes included uptake of HIV tests, receipt of test results, and CD4 counts at diagnosis. We conducted head-to-head comparisons as is for meta-analysis and indirect comparisons in a network meta-analysis using a Bayesian framework.

Our analysis showed that rapid HIV approaches were more effective compared to conventional testing and this is consistent with what has been reported by previous authors. Due to smaller sample sizes and number of available studies, the estimates from our network meta-analysis were not precise and had wide confidence intervals crossing the line of no effect. Owing to this while there is suggestion that for receipt of test results, location based rapid HIV test had greater effectiveness compared to facility based rapid testing, we would interpret this with caution.

The second study of this dissertation, titled “Rapid HIV testing options versus conventional HIV testing: A systematic review of economic evaluations” is a systematic review of published economic evaluations of rapid HIV testing approaches compared with conventional HIV testing being prepared for journal submission. The manuscript summarized the existing literature on cost effectiveness of the use of various rapid HIV testing approaches relative to conventional HIV testing. Included studies were from high income, low prevalence countries in North America, Australia and Western Europe that

have similar HIV epidemiology. Five studies were identified and included in the analysis and results from this review confirm there is evidence to support the continued use of rapid HIV testing for population-based programming.

We also conducted a quality assessment of the included studies using the Drummond criteria and this showed that the studies were of moderate to high quality. We did not conduct a quantitative analysis of the various studies because they reported on different outcomes making combination of these estimates difficult.

A concern noted in the included reviews was the traditional approach of ‘a QALY being a QALY’ taken by the authors. This is consistent with the idea that all potential benefiters from health care are considered equal however there are other authors who consider the need for clear considerations of equity factors in economic evaluations. Cookson et al have suggested a number of approaches to deal with this including applying equity weights to health outcomes, analysis of the opportunity cost of equity, conducting a health inequality impact assessment and a review of the background of information on equity (104,127).

In theory, incorporation of equity consideration in economic evaluation would provide economic evidence of effectiveness of interventions for different segments of the population stratified by equity considerations. The practice, however, is likely to be impractical for a few reasons. These include the current lack of an accepted method of incorporating these equity factors in an economic evaluation. Second, given the possibility there may exist more than one equity consideration in an individual or group of persons, the question arises as to how these equity factors interact and how would

they be combined in an evaluation. Finally, it is unclear at this time if there is a hierarchy of equity factors.

The final manuscript is an economic evaluation where a new model was developed to assess the cost effectiveness of various rapid HIV testing approaches versus conventional approaches as well as the comparative cost-effectiveness of various rapid testing approaches. A discrete event simulation modelling approach was used. The model compared the projected lifetime clinical and economic consequences of persons at risk for HIV who tested various testing options.

The first two manuscripts reviewed and synthesized the evidence for effectiveness and economic justifications for the use of rapid HIV testing in low prevalence high-income settings. The third study of this dissertation titled “Economic evaluation of HIV testing - A discrete event simulation” investigated the cost-effectiveness of the various HIV testing approaches through a health system perspective. We employed a discrete event simulation (DES) modelling approach developed in Microsoft Excel to describe clinical progression of HIV patients diagnosed using different testing approaches over time.

Our modelling considered three HIV testing approaches namely conventional HIV testing and two rapid HIV testing approaches, and we found that for population-based programming standpoint for individuals at increased risk for HIV living in high-income, low HIV prevalence countries, the more cost-effective testing option is the use of rapid facility-based HIV testing.

Strengths and limitations

In each of the manuscripts, we include the strengths and limitation identified. The section below provides a summary of identified strengths and weaknesses.

First, our strengths. This thesis combined a strong health economic evaluation and health services research methodologies providing three manuscripts that have applicability in real-world use for decision and policy makers.

Manuscript 1 provides a quantitative assessment of the clinical effectiveness evidence beyond head-to-head comparisons and considers indirect testing comparisons of the various rapid testing approaches with conventional HIV testing.

The second manuscript provides additional summary of the state of cost effectiveness knowledge for the use of rapid HIV testing approaches. In addition to providing a summary of the evidence, both manuscripts provide an assessment of the quality of included studies.

Finally, the third manuscript is an economic evaluation of rapid HIV testing approaches compared to conventional testing. This de novo economic model as far as is known is the first economic evaluation from a Canadian health system perspective that models the cost effectiveness of the various HIV testing approaches through the various disease stages. The discrete event simulation modelling approach used has a few advantages including the suitability for modelling complex disease conditions while also accounting for other competing health events that may affect on our conclusions.

Additionally, the use of discrete event simulation addresses some of the limitations usually encountered when using other modelling approaches such as state transition

models including the need for tunnel states, need for half-cycle corrections and handling of heterogeneity within the population of interest.

Furthermore, the estimates used to populate our model were derived from the existing literature including the second manuscript and we accounted for the uncertainty that may exist around each of these estimates using the appropriate probability distributions.

The dissertation is not without its limitations and it is acknowledged that there was a relative lack of studies resulting in few studies included in the systematic reviews and network meta-analysis for the first and second manuscripts. Of the studies identified and included, most were from the United States, but we expect that due to the similar disease epidemiology in countries that have this characteristic, the conclusions reached should be applied with caution.

The relative lack of studies also prevented us from quantitatively assessing the relative effects of rapid mobile HIV testing approaches. We also did not consider evidence from saliva based HIV testing options because of lower sensitivity associated with this option resulting in an increased number of false negative result. The lack of studies considering these two options is a missed opportunity given both approaches have potential to be significant in HIV programming.

Finally, there are no studies in this review that considered long term impacts of HIV testing approaches and ensured that we could not comment of outcomes such as treatment response or long-term viral suppression.

Policy and future research implications

Rapid HIV testing continues to be used in HIV diagnosis and this study has provided some evidence for its continued use and potential scale-up. The economic evaluation demonstrated that the use of rapid facility-based HIV testing was more cost effective compared to rapid location-based approaches and conventional HIV testing. This may suggest that against the backdrop of limited health care resources, when considering rapid location-based HIV testing and rapid facility-based HIV testing, the focus should be on the latter based on the available evidence.

While the economic evaluation showed that rapid facility-based testing was more cost-effective, reasons why this is the case are not immediately clear and would benefit from further studies.

Since we were unable to assess the cost effectiveness of rapid mobile HIV testing options, this represents an area that would warrant further study. Additionally, it would be beneficial if the impact of the various testing approaches on long-term patient outcomes would be beneficial.

Finally, in an ideal world, the conclusions would be based on evidence that is more complete rather than on assumptions that we used. Data on disease progression among Canadian patients, Canadian specific testing approach effect measures and more specific disease stage cost and resource utilization would be beneficial to populating a model and this would help derive more specific estimates that would better inform policy makers.

Conclusion

The three studies that were presented confirmed the importance of the use of rapid HIV testing approaches and emphasized the use of rapid facility-based testing was an effective population HIV testing option.

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