HIV, Tuberculosis, and Noncommunicable Diseases: What Is Known About the Costs, Effects, and Cost-effectiveness of Integrated Care?

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Abstract: Unprecedented investments in health systems in low- and middle-income countries (LMICs) have resulted in more than 8 million individuals on antiretroviral therapy. Such individuals experience dramatically increased survival but are increasingly at risk of developing common noncommunicable diseases (NCDs). Integrating clinical care for HIV, other infectious diseases, and NCDs could make health services more effective and provide greater value. Cost-effectiveness analysis is a method to evaluate the clinical benefits and costs associated with different health care interventions and offers guidance for prioritization of investments and scale-up, especially as resources are increasingly constrained. We first examine tuberculosis and HIV as 1 example of integrated care already successfully implemented in several LMICs; we then review the published literature regarding cervical cancer and depression as 2 examples of NCDs for which integrating care with HIV services could offer excellent value. Direct evidence of the benefits of integrated services generally remains scarce; however, data suggest that improved effectiveness and reduced costs may be attained by integrating additional services with existing HIV clinical care. Further investigation into clinical outcomes and costs of care for NCDs among people living with HIV in LMICs will help to prioritize specific health care services by contributing to an understanding of the affordability and implementation of an integrated approach.

Key Words: HIV/AIDS, noncommunicable diseases, cost-effectiveness, integrated care, tuberculosis

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INTRODUCTION

The number of people living with HIV (PLHIV) with access to effective and life-saving antiretroviral therapy (ART) has grown rapidly in low- and middle-income countries (LMICs) over the past decade.[1] Life expectancy has increased,[2–8] and the burden of opportunistic infections has decreased.[9–12] Data from the United States and Europe demonstrate the increasing burden of noncommunicable diseases (NCDs) among PLHIV in the era of ART.[13,14] A similar trend is anticipated in LMICs,[11] where NCDs are already on the rise among the general population (see **Table A1, Supplemental Appendix**, http://links.lww.com/QAI/A545),[15,16] with earlier age of onset and higher mortality compared with higher-income countries.[17,18] PLHIV in LMICs thus represent a population in whom preventive, screening, and therapeutic strategies for NCDs could offer substantial health benefits.[19–21]

Existing HIV infrastructure offers an opportunity to address NCDs and their risk factors.[2,22–24] To date, integration strategies have focused primarily on tuberculosis (TB), sexually transmitted infections, malaria prevention, and reproductive health,[25–28] with some accompanying evaluations of cost-effectiveness.[29] To determine the potential value of integrating clinical care for HIV and NCDs, it is critical to first assess the effectiveness of such integrated interventions. Additional questions then follow: Is the integrated approach cost-effective compared with the current nonintegrated care? Is it affordable? How can it best be implemented in a specific setting? Health economics offers useful methodologies to answer these questions and prioritize efforts. Here, we provide an overview of these methodologies and the data needed for such analyses.

Search Strategy and Selection Criteria

We searched the databases of PubMed and Ovid for studies published in English before January 30, 2014.

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We used the search terms: "HIV," "tuberculosis," and "noncommunicable diseases" as the first set of terms, with "cost-effectiveness," "costs," "integration," and "Africa" in subsequent searches. We also searched for specific NCDs such as "cervical cancer," "depression," and "hypertension." We then used the bibliographies of relevant articles to expand the list of eligible articles.

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis (CEA) and mathematical modeling provide guidance for strategic prioritization of resources by projecting clinical outcomes from specific strategies and examining the comparative value of different strategies. CEA evaluates both effectiveness (eg, in years of life saved) and costs to calculate an incremental cost-effectiveness ratio (ICER; or Δ costs/Δ effectiveness) that quantifies the value of different strategies of care. Guided by recommendations from World Health Organization CHOosing Interventions that are Cost-Effective (WHO-CHOICE),[30] a strategy is often considered "cost-effective" if its ICER is less than 3 times the country-specific per capita gross domestic product and "very cost-effective" if its ICER is less than the per capita gross domestic product. Such analyses can inform policy and allocation of resources for HIV guidelines and care.[31–33]

Data Needed

For which specific NCDs will integration with HIV services have the greatest impact? As discussed by Petersen et al[34] in this supplement, leveraging multi-regional research and programmatic HIV cohorts in LMICs can identify the prevalence and incidence of specific NCDs, including their risk factors and attributable mortality.[35–37] The competing risks of different NCDs and HIV infection must be understood to prioritize an expansion of care services for PLHIV.[38,39]

The value of integration depends on the accuracy and availability of screening and prevention strategies, successful linkage to treatment for those who are eligible, and the effectiveness of the treatment. Necessary data include diagnostic test performance (eg, sensitivity, specificity) in settings with different disease prevalence (eg, yielding different positive and negative predictive values), and the risks associated with screening methods.[40] Easily administered, low-cost tests that yield results rapidly—particularly point-of-care diagnostic tests—could be used in integrating NCD screening into HIV care.[41] Access to treatment and risk factor modification after screening and diagnosis will also affect the value of integrating services.[40] Treatment outcomes include effectiveness, relapse, the frequency and severity of treatment-associated adverse events, and quality of life,[42] using either quality-adjusted life years[43] or disability-adjusted life years.[44]

Costs are a major consideration, especially where resources are most limited,[45] and include direct medical costs (eg, diagnostic tests, preventive strategies, treatments) and costs for infrastructure, personnel, training, and monitoring and evaluation activities.[46,47] Adding costs of NCD screening and treatment to already overstretched health services must be weighed against the burden inflicted by NCDs, including the direct costs associated with management of advanced disease and indirect costs such as time costs (eg, lost wages) for those affected.[48] Additionally, integrating NCD services with existing HIV infrastructure could decrease overall costs by taking advantage of efficiencies of scope.

Outcomes of Interest

CEA can use modeling methods to project clinical outcomes and comparative value of interventions for NCD prevention, screening, and management. Although clinical trials largely define outcomes at early time points, models can estimate the clinical impact of interventions in the short and long term. CEA also quantifies the value of one strategy compared with another by projecting the additional clinical benefits attained for resources used.

A related methodology, budget impact analysis (BIA), assesses the costs of a program in specific settings. BIA focuses on program affordability from the perspective of stakeholders, such as ministries of health, nongovernmental organizations, or other payers. These analyses also account for the direct per capita costs of a program and the number of patients treated in a given program over a specified budget period.[48] Thus, although a strategy may be cost-effective when measured against an external threshold of willingness to pay,[30,40,49] BIA assesses the actual resources needed to implement that strategy in a specific setting.

CASE STUDIES

Integrating clinical services offers an opportunity to improve overall health among PLHIV but also has the potential to undermine HIV care. Further investigation will determine whether outcomes will improve or suffer. After a systematic review of the literature, we describe TB/HIV as 1 example of existing integrated services and describe data needed to assess its cost-effectiveness. We then examine cervical cancer and depression as 2 case examples of the potential for integrated NCD/HIV care.

TB/HIV Integrated Services

TB: Epidemiology, Quality of Life, and Mortality

TB in PLHIV offers a prime opportunity to assess the impact and cost-effectiveness of an integrated approach to care compared with distinct treatment sites. Approximately 1.1 million of the 33.3 million PLHIV in the world were diagnosed with active TB in 2012 alone.[50] PLHIV who have TB experience a substantially decreased quality of life[51] and increased stigma,[52] both of which improve with treatment.[53] TB remains the leading cause of death among PLHIV; almost 25% of those with HIV and TB worldwide will die from TB.[54]

TB/HIV: Screening and Treatment Outcomes

Early detection and treatment of TB are critical to reducing TB mortality and transmission among PLHIV.[55–58] Active TB screening results in timely, accurate TB diagnoses for which effective treatment exists.[59–63] However, separate clinical sites for TB and HIV can result in reduced TB or HIV

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case finding and poor (62%) or delayed (32%) linkage to care,[64] and low rates of ART initiation (13%–62%).[64–67]

Integration of TB/HIV services can address these shortcomings.[68–71] In Guatemala, TB/HIV integration improved initiation of TB treatment (23% vs. 94%, pre- vs. post-integration) and decreased mortality at 50 weeks (72% vs. 27%).[70] In Uganda, integration resulted in modest gains; more patients completed TB treatment (62% vs. 68%, pre- vs. post-) and fewer experienced death or treatment default (33% vs. 25%).[71]

Integrated TB/HIV care could lead to improvements not only in TB but also in HIV outcomes.[72] In the Democratic Republic of Congo, 46% of TB patients preferred HIV counseling/testing by TB nurses rather than referral to a free-standing HIV voluntary counseling/testing site (25%) or a separate, on-site clinic (29%).[73] In a Ugandan study, patients were more likely to initiate ART at some point during TB treatment (78% vs. 94%), especially during the earlier intensive treatment phase (23% vs. 60%).[71] In an integrated South African site, time to ART initiation decreased from 147 days to 75 days, and patients were 1.6 times more likely to start ART.[74]

TB/HIV: Costs

Although the direct costs of TB and HIV care have been reported,[75,76] the detailed costs and tradeoffs of integrated TB/HIV care are not yet well described. In addition to diagnostic tests and medications, costs include infrastructure, personnel, and training.[77] Integrated TB/HIV care could reduce overall resource utilization by relying on efficiencies of scope to increase the value of existing infrastructure and personnel.

Cost-effectiveness of TB/HIV Integration

Several studies have examined the cost-effectiveness of specific aspects of integrated TB/HIV care. Integrating routine HIV testing into TB treatment clinics in India is "very cost-effective" when compared with selective screening[78] and is likely to be even more cost-effective in settings with higher HIV prevalence because more people are likely to be diagnosed with HIV and linked to care.[59,79,80] Integrating TB screening methods (eg, Xpert MTB/RIF or urine LAM) when initiating ART for PLHIV can be cost-effective in South Africa as compared with symptom screening and sputum smear or sputum culture.[81–83] Point-of-care tests that improve linkage to care could outweigh limitations in test characteristics, such as reduced sensitivity or specificity, when compared with a laboratory-based test.[84] Isoniazid preventive therapy among PLHIV offers another example of how integrating an aspect of TB prevention into HIV services can be cost-effective.[80,85–87]

OPPORTUNITIES TO INTEGRATE HIV AND NCD CARE: USING A COST-EFFECTIVENESS APPROACH

In terms of value, data are limited but promising regarding the impact on NCD outcomes of integrating HIV care into primary care.[22,88,89] Screening for NCDs and their risk factors, as well as associated treatments, fall along a wide spectrum regarding continuity of care and costs (see **Table A3, Supplemental Appendix**, http://links.lww.com/QAI/A545). Interventions are more costly if they require intensive training or the use of new technologies or if they occur at frequent intervals among large numbers of people. Cervical cancer and depression are 2 examples of NCDs that merit further evaluation regarding the potential value of integration.

CERVICAL CANCER/HIV INTEGRATED SERVICES

Cervical Cancer: Epidemiology

As further described by Adebamowo et al in this supplement,[90] invasive cervical cancer (ICC) will likely be a major cause of mortality as women living with HIV gain increased access to ART in sub-Saharan Africa (SSA).[91,92] The incidence of ICC in SSA is the highest in the world; age-standardized incidence rates in the general population range from 28 to 42.7 cases per 100,000 women.[91] HIV-infected women are at even greater risk for ICC,[93–96] which often occurs at younger ages[97] and presents at more advanced stages when treatment is less likely to be successful.[98] Furthermore, ART may not reduce cervical cancer risk, and life-long screening is needed.[98,99]

Cervical Cancer: Screening and Treatment Outcomes

ICC often manifests with precursor cervical lesions evident with screening and amenable to treatment. Multiple screening methods have demonstrated accuracy in LMICs,[91,100] with the ability to incorporate mobile technologies[101,102] and well-trained nonphysician clinicians to extend services.[97,102,103] Likewise, when precancerous lesions are identified, multiple treatment options demonstrate excellent efficacy in LMICs.[102,104–108] Operational aspects of screening and treatment for ICC and its precursor lesions have been demonstrated in Zambia, with more than 65,000 women screened in the first 5 years of a large program[109,110] and more than 110,000 women screened over the past 8 years.[111]

Although screening is available and accurate, only 0.4%–20.2% of African women receive even 1 screening test in their lifetimes.[91,102,112,113] Loss to follow-up after initial diagnosis is high, and treatment opportunities are missed.[97,114] Integrating ICC screening and treatment with HIV services could offer improved uptake of screening and treatment outcomes.

Cervical Cancer: Costs

Studies have reported on the costs of reagents, technologies, and infrastructure for cervical cancer screening programs in LMICs, including cytology ($2.0–4.4 per specimen), human papillomavirus DNA testing ($7.9–8.6 per test), and visual inspection with acetic acid (<$5 per test).[115,116] Costs for staff, training, and quality assurance of procedures have not been reported, and the efficiencies of scope attained with integration of services have not yet been established.

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Cost-effectiveness of Cervical Cancer and HIV Integration

Although extensive literature exists on the cost-effectiveness of screening interventions to reduce ICC among the general population in LMICs[117–121] and among PLHIV in high-income settings,[122] cost-effectiveness literature is limited regarding ICC in PLHIV in LMICs. A study from Brazil suggests that a 2-tiered screening approach (ie, annual human papillomavirus screening followed by cytology, if positive) is very cost-effective in HIV-infected women[123]; integrating such an approach into routine HIV care could further increase its value if outcomes are maintained and uptake improved. An analysis in SSA suggests that only 262 HIV-infected women receiving ART would need to be screened to prevent 1 cervical cancer death.[124] Integration with HIV services and the utilization of existing infrastructure have the potential to facilitate scale-up and decrease barriers to access.[114,125]

DEPRESSION/HIV INTEGRATED SERVICES

Depression: Epidemiology and Quality of Life

Depression is highly prevalent among PLHIV in SSA, requiring repeated screening and longitudinal treatment, as described by Chibanda et al[126] in this supplement. Up to 40% of PLHIV attending ART clinics in LMICs suffer from depression,[127–134] and specific subgroups, such as women, are at particularly high risk.[135–138]

Depression can negatively impact adherence to ART, leading to worse HIV outcomes.[130–132,139–143] In a meta-analysis from SSA, ART adherence was 55% lower in patients with depression symptoms.[134] Women with HIV who reported symptoms of depression also experienced accelerated HIV disease progression and higher mortality.[138] Depression among PLHIV has been correlated with reduced quality of life in the United States,[144] and early evidence suggests the same in SSA.[145]

Depression: Screening and Treatment Outcomes

Simple screening strategies for depression are feasible in LMICs and in HIV-infected populations, offering an opportunity for integration.[146,147] Short surveys have been validated in HIV-uninfected populations,[148] as have longer surveys[149] and visual scales.[150] Incorporating screening for substance use, especially alcohol use, could offer particular benefit, given its comorbidity with both HIV and depression.[151,152] Integration of depression screening with HIV care could improve case detection and management.[153]

Treatment options for depression exist in LMICs. Medications, cognitive behavioral therapy, and interpersonal therapy have all been studied in PLHIV in LMICs.[147,154–156] Further study is needed on the accessibility and sustainability of these interventions, the quantification of their impact on quality of life and life expectancy, and their integration into routine HIV care.[139]

Depression: Costs

Costs of screening for and treating depression include personnel, training, therapy, and associated medications, which could offset other medical costs from utilization of health services and improve economic outcomes in treated patients.[157–159] If successful diagnosis and treatment of depression increased ART adherence or retention in care, then costly second-line ART regimens could be deferred or avoided. However, the scale of such benefit is unclear.

Cost-effectiveness of Depression/HIV Integration

In high-income country general populations, CEA has demonstrated that integrating depression screening and treatment with primary care can be cost-effective.[157,158] Decreased overall costs of care can be achieved by integrating care for HIV, mental health, and substance use in the United States; longer follow-up for such interventions will provide more data about the sustainability of such an approach.[159] This question, to our knowledge, has not yet been studied in LMICs.

TRADEOFFS AND CHALLENGES ASSOCIATED WITH IMPLEMENTATION OF INTEGRATED SERVICES

The optimal implementation of integrated strategies in specific settings remains to be determined,[160] and integrated care could have unintended consequences. Wait times increased from 91 to 127 minutes in a Zambian clinic because of staff and patient flow problems after integration of HIV services with primary health care.[161] Longer wait times could increase loss to follow-up or exacerbate stigma,[162–164] and TB transmissions could even be increased.[69,165] Staff training and program quality might be less effective or more costly when multiple interventions are provided together.[166] Developing quality indicators for NCD and HIV outcomes will assist in programmatic feedback and assessment of these potential tradeoffs.[166–169]

The benefits of introducing integrated services and new technologies can be realized only if accompanied by initiatives that strengthen health systems, as emphasized by the Gene Xpert experience in South Africa.[170–172] Any value of integrating NCDs or TB with HIV clinical care will only be achieved if health systems are capable of providing high-quality clinical care consistently and rapidly.

Integration of NCD/HIV services could build on innovative approaches from a diversity of tools and experiences. The expanded use of mobile health (mHealth) suggests that information technologies can improve effectiveness and decrease costs for integrated care.[101,173,174] Analyses of primary health clinics in LMICs, which face similar challenges in terms of a management of diverse comorbidities, can offer guidance regarding NCD care for PLHIV.[175] NCD screening and treatment could be included in decentralized public health clinics, mobile clinics, community-based campaigns, or home-based care, which may offer additional opportunities for accessing those absent from clinics and allow for increased coverage by integrated services.[176–180] Although integration and expansion of NCD care within HIV services can be implemented more easily in settings with more

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established health care infrastructures,[181] integration may offer even more clinical benefits in the most resource-limited settings where NCD services are not yet routinely available. Barriers to access and methods to facilitate scale-up need investigation in specific clinical settings.

RESEARCH AND TRAINING AGENDAS

To assess the value of different strategies for screening, prevention, and management of NCDs among PLHIV in LMICs, innovative research at the intersection of NCDs and HIV in LMICs is warranted (Table 1). Data needed include the incidence and prevalence of various NCDs among PLHIV in LMICs, screening and treatment outcomes, effects of NCDs on quality of life in PLHIV, and the costs associated with managing these comorbidities. The specific assessment of integrated services and the implementation of best practices are also critical.

Clinical training of health care workers for NCD screening and treatment is necessary,[167,182] as is further training of students and health professionals in epidemiology and implementation science.[183] As new programmatic initiatives are developed for NCDs in LMICs, formal training in costing methodology, CEA, and BIA will offer opportunities for capacity building to assist policymakers at local, regional, and national levels.

SUMMARY AND CONCLUSIONS

The remarkable success of ART scale-up in LMICs has established an infrastructure for providing longitudinal medical care to millions of people. PLHIV are living longer and healthier lives but are now at risk for morbidity and mortality from NCDs. The clinical impact and costs of different strategies for NCD prevention, management, and diagnosis in PLHIV is beginning to be quantified. Implementation science can inform the adaptation and expansion of lessons learned from HIV and TB/HIV integrated care to NCDs. Optimal strategies will vary by country, setting, and the underlying burden of different NCDs. Cost-effectiveness and BIA, in addition to observational studies and randomized clinical trials, are complementary tools to assess the value of screening for and treatment of NCDs and can inform health policy in an era marked by very effective HIV therapy, a growing NCD burden, and increasingly limited resources.

TABLE 1. Research Agenda on the Cost-effectiveness and Implementation of Integration of NCD Management With HIV Care for People in LMICs

To assess the cost-effectiveness of NCD management for PLHIV in LMICs, collect data on:
Epidemiology: to determine prevalence, incidence, and attributable mortality by demographics and region
Quality of life: to examine the impact of comorbid NCD diagnoses and their treatments
Screening: to evaluate the test characteristics, yield, and outcomes
Treatment: to assess the availability and outcomes of NCD management strategies
Costs: to quantify the resource use of screening, treatment, and management of NCD clinical outcomes
To investigate optimal strategies for integration of expanded screening and treatment of NCDs in PLHIV, collect data on:
Outcomes: to measure clinical and economic outcomes with both distinct and integrated care
Time points: to determine short-term and long-term outcomes, including linkage to and retention in care
To use existing clinical and research platforms, extend research training in LMICs in the following fields:
Clinical epidemiology
Implementation science
CEA
Mathematical modeling

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