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Modeling the cost–effectiveness of HIV treatment: how to buy the most 'health' when resources are limited

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Abstract

Purpose of review—To summarize recent cost–effectiveness analyses (CEAs) that evaluate optimal treatment strategies for persons living with HIV/AIDS (PLWHA).

Recent findings—Efforts to attain universal coverage of current treatment guidelines (e.g., initiation at $CD4^+$ cell count <350 cells/μl) are generally very costeffective. Expansion of access beyond current guidelines will additionally improve clinical outcomes and aversion of new HIV infections; however, cost–effectiveness is more uncertain. Increasing access to antiretroviral therapy (ART) offers greater health benefit than investing the same funds in intensive laboratory monitoring for those on ART, particularly in those settings in which universal coverage has not yet been attained. Recommended ART regimens (e.g., tenofovir) have favorable cost–effectiveness when compared with substitution of newer, more expensive agents (e.g., rilpivirine, darunavir) or substitution of older, cheaper alternatives that are more toxic (e.g., stavudine).

Summary—There is increasing use of CEA to evaluate decisions regarding HIV treatment in order to buy the most 'health' with limited resources. Expansion of ART access provides substantial clinical and preventive benefit and offers favorable cost–effectiveness. Intensive laboratory monitoring may not be the highest priority in settings in which resources are constrained. Further work on the economic impact, clinical effectiveness, and feasibility of ART treatment for all (e.g., no $CD4^+$ cell initiation criteria) is needed.

Keywords

antiretroviral therapy; cost–effectiveness; HIV/AIDS; mathematical modeling

INTRODUCTION

Antiretroviral therapy (ART) effectively prolongs and improves life of HIV-infected individuals in the developing [1,2] and developed world [3,4]. More than 25 antiretroviral

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agents have been approved and new therapeutics are arriving rapidly. However, substantial economic challenges remain a threat to the global fight against the disease [5–7].

In order to simultaneously address these clinical and economic challenges, it is important to evaluate how to obtain the optimal clinical outcomes with the limited resources available. Cost–effectiveness analysis (CEA) and mathematical modeling (which can estimate outcomes over clinically relevant time periods) are methodologies that have provided insight into optimizing and prioritizing healthcare services [8]. These analyses integrate information on efficacy, cost, and individual-level and population-level outcomes, and thereby predict how to get the most ‘bang’ (that is, healthcare benefit) for the available healthcare ‘buck’ (that is, available resources). CEAs generate outcomes of incremental cost– effectiveness ratios (ICERs; cost per unit of health gained). Larger numbers are less favorable because they signify less health is generated per unit of resources spent, whereas smaller numbers are more favorable because they signify more health is generated per unit of resources spent.

In this article, we briefly review model-based CEAs published in the past 2 years that evaluate aspects of treating HIV/AIDS. We used the Medline online database to conduct a literature search of articles published between January 2011 and June 2013 using key words ‘cost–effectiveness’, ‘HIV’, ‘antiretrovirals’, ‘ART’, and ‘opportunistic infections’. We excluded studies that did not utilize mathematical modeling, did not include an economic or CEA, and were not published in English.

We did not strictly perform a systematic review; rather, we deliberately emphasize studies that are most relevant to programmatic decisions being faced by decision-makers ‘out in the field,’ and stakeholders and funders of HIV care and research. We cast particular attention on studies that sought to compare methods to attenuate tuberculosis (TB) and other opportunistic infections among the HIV infected; compare when to initiate ART; compare alternative first-line antiretroviral regimens; compare alternative strategies for screening and monitoring the success of ART; and compare and evaluate the impact of ART through secondary effects on transmissibility of HIV.

EVALUATION, SCREENING, AND PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS AMONG HIV-INFECTED PERSONS ELIGIBLE FOR ANTIRETROVIRAL TREATMENT

Persons living with HIV/AIDS (PLWHA) often present with advanced immune suppression. Therefore, even among those who initiate ART, there are high rates of short-term mortality because of a variety of opportunistic infections in sub-Saharan Africa, especially because of TB [3,9].

Tuberculosis

TB, in particular, is implicated in more than 60% of deaths of HIV-infected South Africans [10]. Indeed, up to 30% of newly diagnosed HIV infections may coexist with active TB [11].

Recent advances in TB diagnostics such as the Xpert MTB/RIF assay, a PCR-based tool, may improve diagnostic accuracy for TB in newly diagnosed PLWHA [12]. Andrews et al. using the International Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model [13■] showed that screening all newly diagnosed patients regardless of symptoms with Xpert MTB/RIF was very costeffective (<1 GDPpc of South Africa; US$7100) if TB prevalence was more than 8% and remained cost-effective (<3 GDPpc) at lower TB prevalence [13■]. Abimbola *et al*. [14] found that Xpert screening prevented more deaths at lower cost compared with current practice among PLWHA in sub-Saharan Africa presenting for care. Menzies *et al*. [15■] used an epidemic model of TB and found Xpert for suspected TB cases in sub-Saharan Africa had a very favorable ICER of US$784 to US$959 per disability adjusted life year (DALY) averted. In contrast to these favorable findings for Xpert, implementation of mycobacterial culture for TB diagnosis, a WHO-recommended strategy [16], had an unfavorable ICER of US$60 430 per TB death averted compared with the Xpert strategy.

In summary, although these studies overall suggest that Xpert screening is likely to be cost-effective and potentially cost-saving, not all considered start-up costs for the implementation of Xpert, or empiric treatment of TB among those who test negative but for whom clinical suspicion exists. These factors likely contribute to an overestimation of the cost–effectiveness of Xpert in relation to current practice as suggested by these CEAs.

WHEN TO INITIATE TREATMENT?

Guidelines for ART have progressed toward earlier treatment [17–19], and multiple CEAs have found earlier ART to be costeffective in both developed and developing world settings [13■,20–25]. However, implementation of the current ART WHO guidelines ($CD4^+$ cell count ≤350 cells/μl) has been incomplete because of limited resources or concerns about its value [26].

Bor *et al*. [27■] using primary data analysis extrapolated the population level impact of the public sector ART program in South Africa, estimating a favorable cost–effectiveness of US $1593 cost per life year. Sempa et al. [28■] found that earlier initiation (starting ART when CD4■ cell count ≤350 cells/μl compared with <200 cells/μl) was very costeffective in Uganda, averting a DALY for as little as US$260 (GDPpc US$490). However, this study did not account for treatment failure and progression to more expensive second-line ART, which may have biased the results in favor of earlier therapy. Mills et al. [29■] compared early ($CD4^+$ cell count ≤350 cell/μl) versus delayed ($CD4^+$ cell count ≤200 cells/μl) ART initiation in Uganda and found a favorable ICER of US$695 per life-year gained, but this estimate was sensitive to assumptions about ART program costs.

In summary, CEAs suggest that earlier ART initiation (up to $CD4^+$ cell count ≤500 cells/μl) may offer favorable value, although estimates are sensitive to costs of subsequent ART regimens.

WHAT TO INITIATE TREATMENT WITH?

Despite prior evaluations of ART regimen recommendations by expert international bodies, questions remain as to the specific regimens and drugs that provide the optimal benefit for the resource expended, especially as the armamentarium of anti-retroviral agents continues to grow.

Older regimens

WHO guidelines have recommended against stavu-dine (d4T) for first-line ART due to its toxicity [19]. However, d4T + lamivudine (3TC) + nonnucleoside reverse transcriptase inhibitor [NNRTI; nevirapine (NVP) or efavirenz (EFV)] is inexpensive, so its use has been widespread. Fortunately, the cost and toxicity tradeoffs have been subject to CEA. Bendavid *et al*. [30■■] found that d4T-based ART was not costeffective compared with other first-line regimens. Tenofovir (TDF)-based regimens were cost*effective, with ICERs per QALY gained of US$1045 and US$5950 for TDF + 3TC + NVP and TDF + 3TC + EFV, respectively (South Africa GDPpc US$5800). Similarly, Jouquet *et al*. [31] estimated a favorable ICER (US$835 per QALY gained over a 1-year period) for a TDF-based regimen compared with d4T-based regimen in Lesotho. Additionally, TDF-based first-line ART regimens show more favorable cost–effectiveness compared with zidovudine (AZT)-based first-line ART. While many CEAs have not accounted for HIV drug resistance generation [30■■,31,32], von Wyl *et al*. [33■■] employing explicit modeling of ART resistance generation, also demonstrated that TDF-based first-line ART would be very costeffective or cost-saving compared with AZT-based first-line regimens in a developing world setting.

Newer regimens

A number of newer antiretrovirals (e.g., 2nd generation NNRTIs, 3rd generation protease inhibitors, and new classes such as integrase inhibitors) have been approved for use in resource-rich environments. Simpson *et al*. [34■] compared a darunavir-based protease inhibitor regimen (3rd generation protease inhibitor) to a lopinavir (LPV/r)-based pro-tease inhibitor regimen (2nd generation protease inhibitor) in an industrialized setting and found LPV/r-based first-line ART associated with lower costs yet similar clinical outcomes. Simpson *et al*. [35] found that LPV/r-based first-line ART had favorable cost–effectiveness compared with an atazanavir-based (ATZ/r) regimen (ICER per QALY gained, ATZ/r versus LPV/r, US$234 180). Finally, Bonafede *et al*. [36] studied NNRTI-based first-line regimens, and found that EFV is cost-saving compared with the newer second-generation drug rilpivirine. These studies suggest that current recommendations for initial ART regimen have favorable cost–effectiveness in resource-rich environments, and likely also in resource-limited environments.

Fixed dose combinations and generic drugs

Because the cost for treating PLWHA is projected to increase [37], it is increasingly important to identify greatest value for the resources expended. Using the CEPAC model, Walensky *et al*. [38■■] found that the use of coformulated trademarked ART regimen(s) was associated with unfavorable ICERs more than US$100 000 under most conditions when compared with three-drug generic based ART within the USA, an estimate that certainly

portends unfavorable cost–effectiveness in resource-limited settings [39]. Indeed, utilizing generic based ART could save US$920 million compared with branded ART regimens if all eligible US patients switch or start these regimens, so generic based ART may offer favorable cost–effectiveness worldwide.

OPTIMAL MONITORING STRATEGY FOR ANTIRETROVIRAL THERAPY

As ART programs expand, decision-makers may need to compare the benefit provided by earlier and/or higher coverage ART with the benefit provided by using those resources alternatively on more intensive laboratory monitoring. Indeed, routine laboratory monitoring of patients on ART in developing world settings (i.e. q3 month toxicity and $CD4^+$ cell evaluations) was demonstrated to be an inefficient use of resources (ICER of US$7,793 per QALY gained) compared with clinically driven monitoring [40■], even though this CEA did not even consider the most expensive monitoring option available, viral load.

Routine viral load monitoring

Prior studies have had conflicting results on the cost–effectiveness of viral load monitoring for patients on ART in resource-limited regions [41–43], and more recent analyses have provided additional information. Hamers *et al*. [44■] found that when compared with $CD4^+$ cell testing every 6 months, viral load monitoring every 12 months was found to dominate (i.e., greater clinical benefit at lower cost), whereas viral load monitoring every 6 months was associated with an ICER of US$85 per QALY gained. Braithwaite *et al*. [45■] evaluated multiple monitoring strategies including contingent viral load (depending on $CD4^+$ cell count), routine viral load, and routine $CD4^+$ cell strategies under different ART availability scenarios. $CD4^+$ cell monitoring alone was never a preferred strategy regardless of ART availability. In addition, although routine viral load monitoring could be considered costeffective under certain willingness to pay scenarios, it was never more costeffective than the value achieved by initiating more persons on ART (by increasing eligibility to all persons with $CD4^+$ cell count <350). Even though regular viral load monitoring lowered resistance accumulation (by ~20% after 5 years), increased median $CD4^+$ cell count (by 20 cells/ml after 5 years), and lowered viral load (by ~0.4 log units after 5 years), these benefits were not of sufficient clinical significance to offset the opportunity cost of failing to place more people on earlier ART, which had more dramatic effects on improving $CD4^+$ cell count and viral load. Estill *et al*. [46■] found comparable results for the cost–effectiveness of point-of-care viral load testing in South Africa to those of Braithwaite et al. Levison *et al*. [47■] evaluated inclusion of HIV genotype testing at diagnosis of first-line treatment failure using the CEPAC model and found this strategy to be very costeffective (ICER US$900 per life year saved) within a simulated cohort of HIV-infected adults at first-line treatment failure. However, this model did not consider the possibility of second-line ART as a salvage mechanism, so its applicability is unclear. Additionally, if associated delays in care are significant, this strategy would not be preferred.

Although the results of these analyses are not always consistent because of different model assumptions, costs, and inputs, nearly all studies suggest more intensive monitoring for virological failure may be a cost-effective intervention except in an environment of

competing priorities, particularly if not all patients with $CD4^+$ cell count less than 350 have been started on ART.

EPIDEMIC MODELING, SECONDARY EFFECTS, AND THE COST–EFFECTIVENESS OF ANTIRETROVIRAL THERAPY

It is well established that ART-induced viral suppression decreases HIV transmissibility in heterosexual relationships [48,49]. However, most CEA modeling studies have not accounted for the potential impact of ART on the transmissibility of HIV to uninfected persons (secondary effects of ART). Fortunately, recent work has explicitly addressed the impact of alternative ART decisions on secondary infections and on the pandemic in general, provocatively identifying circumstances (though highly improbable) in which the HIV epidemic could be eliminated [50–54].

Granich *et al*. [55■■] projected that 'treatment as prevention' (TasP) or in other terms treatment for all HIV-infected persons would be associated with substantial upfront costs, but would be cost-saving after 10 years. In comparison to current WHO guidelines in South Africa (80% ART coverage for all HIV-positive with $CD4^+$ cell count ≤350 cells/μl [19]), TasP (80% coverage for all HIV-infected) would reduce the number of new HIV infections by an additional 39% and by 40 years save an additional US$6 billion (assuming improvements in prevention over time). However, these findings may be setting-specific as they assumed low ART cost, high inpatient costs, and an optimistic proportion of HIV infections averted.

In contrast, Wagner and Blower [56■■] employed an epidemic model with more explicit accounting of viral resistance and utilization of second-line ART. Although the epidemic projections were similar to those stated by Granich *et al*., they had starkly differing economic predictions including greater cumulative costs over 40 years and prohibitive up-front costs (for TasP compared to universal access). Other CEAs have questioned whether the TasP approach is preferable in a resource-limited setting in which there may be competing priorities for investment with other proven HIV treatment and prevention interventions. For example, studies have suggested that expansion of medical male circumcision in the developing world alongside achievement of WHO goals for ART access might provide more value (and potentially may be more feasible to achieve) than the implementation of a TasP approach [57■■,58■].

In summary, CEAs evaluating expansion of ART access utilizing an epidemic approach have demonstrated an impressive population level impact of TasP, but have yielded mixed results on the economic feasibility of implementing such strategies, especially in resource-limited settings.

CONCLUSION

There has been a growing body of literature using CEA and mathematical modeling to estimate the population health effect and cost–effectiveness (cost per benefit) of various HIV management strategies. Although these studies are methodologically heterogeneous,

some commonalities emerge, and are described in the 'key points' below. Perhaps most importantly, expansion of ART at least to levels currently recommended by the WHO should be the highest priority for programs that are facing simultaneous resource constraints, such as difficulty paying for expensive laboratory tests.

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(WHO), the authors also find that ART expansion is very effective. However, authors found a TasP strategy in South Africa could eliminate HIV, but take 40 years (as compared to 10) and cost approximately US$12 billion more than achieving universal access of ART for those with $CD4^+$ cell count 350 cells/μl or less (as compared to US$10 billion less).]

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KEY POINTS

- Universal access to ART following the 2010 WHO guidelines has been consistently demonstrated to be costeffective and may even be cost-saving compared with current practice.
- In settings that have not yet fully implemented WHO guidelines because of resource constraints, scaling up ART will provide more health than using the same resources on more aggressive laboratory monitoring.
- Accounting for the secondary effects of ART on HIV transmissibility can improve the economic impact of ART expansion and is necessary in order to make informed policy decisions regarding access.
- Currently recommended ART regimens provide greater value routinely than use of many of the newly approved drugs for the treatment of HIV/AIDS.
- There are further opportunities to increase the cost–effectiveness and/or value of HIV treatment both in the industrialized and developing world, including routine use of generic ART and improved screening for opportunistic infections.