The HIV cure research agenda: the role of mathematical modelling and cost-effectiveness analysis

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Abstract

The research agenda towards an HIV cure is building rapidly. In this article, we discuss the reasons for and methodological approach to using mathematical modelling and cost-effectiveness analysis in this agenda. We provide a brief description of the proof of concept for cure and the current directions of cure research. We then review the types of clinical economic evaluations, including cost analysis, cost-benefit analysis and cost-effectiveness analysis. We describe the use of mathematical modelling and cost-effectiveness analysis early in the HIV epidemic as well as in the era of combination antiretroviral therapy. We then highlight the novel methodology of Value of Information (VOI) analysis and its potential role in the planning of clinical trials. We close with recommendations for modelling and cost-effectiveness analysis in the HIV cure agenda.

Keywords: HIV/AIDS, cure, mathematical modelling, cost-effectiveness

Introduction

Since the description of the original cases in 1981, AIDS has become the most important global pandemic in recent history, with an estimated 35 million people currently infected with HIV [1]. The advent of effective combination antiretroviral therapy (ART) in 1996 had a dramatic impact on improving survival with HIV, initially in well-resourced and then in resource-limited settings [2,3]. In the past several years, studies demonstrating the efficacy of prevention have added to the armamentarium of strategies for care [4–6]. Recent trials have proven that early ART improves both individual clinical outcomes, and decreases HIV transmission [7–9]. Until recently scientists, policy-makers and civil society organisations have generally not considered the possibility of curing HIV infection. Scientific developments over the past few years, however, suggest that an effective cure might be on the horizon. Research protocols are under way on a broad range of biological approaches, as well as therapeutic strategies, that may lead to either a functional cure (i.e. control of HIV without full elimination, but with no requirement for further ART), or a sterilising cure (i.e. complete elimination of the virus) [10–12]. On World AIDS Day 2014, President Obama committed to providing $100 million for the investigation of HIV cure [13].

In light of this promising research and increasing commitment, issues are already emerging related to the potential cost and cost-effectiveness of plausible HIV cure strategies [14]. Cost-effectiveness, that is, the 'value for money' of any healthcare intervention, is generally compared to a current standard of care. Assessing the potential cost-effectiveness of HIV cure strategies, as well as the value of the information to be derived from future clinical trials of cure strategies, can help guide priority-setting and decisions by governments and other funders towards research into HIV cure.

In anticipation of and alongside clinical trials, mathematical models provide a framework by which the cost-effectiveness of new interventions can be defined. This is because such models can be used to anticipate the future impact of emerging innovations as well as integrate data from a variety of sources once studies are completed. This integration can be used to project outcomes beyond the timeline of the completed studies and assess uncertainty using formal methods [15]. By providing insight into the potential cost-effectiveness of HIV cure strategies, simulation models can be instrumental in highlighting the value of pursuing specific research strategies and informing the design of clinical trials [15].

Challenges for and directions of HIV cure research

The mechanisms by which HIV persists in spite of potent ART are the focus of intense research. Among the multiple mechanisms involved, the most important one appears to be the establishment of HIV latency, when integrated viral DNA is silenced by host mechanisms and the virus cannot be accessed by current ART or by host clearance mechanisms [16]. The primary cellular target for HIV infection is the CD4+ T cell. Most infected cells die rapidly,

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but a small proportion become stably infected with integrated HIV-originated DNA and revert to a long-lived resting phenotype [17]. Additional barriers to HIV cure include the existence of non-T cell reservoirs, such as macrophages, ongoing cycles of HIV replication even in the presence of ART and an immune system that is permanently affected by HIV and cannot adequately clear the virus [18].

Several recent reports, however, have contributed to invigorating research in the field of HIV cure. The report of the 'Berlin patient' is thought to describe the first case of a sterilising HIV cure [19]. This patient received a bone marrow transplant for acute myeloid leukaemia from a donor carrying the protective CCR5Δ32 mutation, and he has now remained free of HIV for 7 years after stopping ART [20]. Important insights have also been gained from identification and characterisation of 'post-treatment controllers.' The French VISCONTI cohort reported on 14 individuals who controlled HIV for nearly 10 years despite discontinuation of ART following treatment started very early after infection [21]. Another promising case was that of the 'Mississippi baby', who received ART 30 hours after birth and maintained undetectable blood and tissue HIV-RNA after ART interruption [22], although after almost 2 years without treatment, she was found to have detectable HIV levels in her blood [23]. A 2013 study reported that bone marrow transplantation with wild-type CCR5 rendered HIV undetectable in two individuals for extended periods; both, however, experienced viral recrudescence after 21 and 42 months [24]. None the less, these reports contribute to the growing evidence that early treatment may be an important factor in limiting the size and distribution of HIV reservoirs [25].

In addition to the above approaches, many other potential strategies for cure are being investigated. Major efforts are aimed at reversing latency and eliminating the cellular reservoir. One approach is the reactivation of transcription of latently integrated viral DNA using the chromatin remodelling enzymes histone deacetylase (HDAC) inhibitors [26]. Related efforts include protein kinase C inducers [27], DNA-methylation inhibitors [28] and interleukin-7 [29]. There is also intense interest in developing methods to either enhance the capacity of the host immune system to clear HIV-expressing cells or to identify therapeutic modalities that target and kill HIV-expressing cells [30]. Therapeutic vaccines and/or immunomodulating drugs, such as anti-PD-1 antibodies, are being pursued for the former approach and HIV-specific monoclonal antibodies linked to an immunotoxin for the latter. Finally, gene therapy approaches using zinc-finger nucleases to modify CD4 cells have provided early evidence that patients may be able to interrupt ART after such CD4 modification [31].

Although it is not yet clear which, if any, of these strategies may prove successful, it is likely that a combined approach of diverse therapeutic strategies will be necessary to achieve an HIV cure [32]. Yet, even as ongoing studies provide insights into potential for cure, important questions will remain. Even if effective, how effective will these strategies be in the short-term? What percentage of patients will relapse over the longer-term? What are the risks, both short- and long-term, of any cure strategy? By using a formal modelling framework and established methods of uncertainty analysis, this approach can help inform policy, even as questions about longer-term outcomes begin to be answered.

Clinical economics and cost-effectiveness analysis

In understanding the role of modelling and economic analysis in HIV cure research, and cost-effectiveness analysis in particular, it is important to distinguish among the different types of economic analysis: cost analysis (or cost-minimisation analysis); cost-benefit analysis; and cost-effectiveness analysis (or cost-utility analysis).

Cost analysis

Cost analysis is a method that estimates the resources used (or costs) for a particular type of care or focused towards a specific illness, such as HIV. The outcome of interest is cost and these studies are generally used for planning and budgeting purposes. A study by Gebo *et al*. described the average cost of HIV care in the US as ~$20,000/person/year [33]. While one of the most important factors in defining the lifetime cost of HIV care is the cost of antiretroviral therapy, total lifetime costs depend on the number of available medications and the types of regimens. While cost analysis is particularly useful for planning purposes, it does not provide insight to the *value* of the interventions utilised in terms of what is gained clinically for the expenditure of costs, either in terms of lives saved, years of life saved, or quality-adjusted life years saved.

Cost-benefit analysis

Cost-benefit analysis incorporates resources for clinical interventions as well as the value of those resources defined in terms of clinical benefits. The outcome measure is monetary; clinical benefits such as years of life saved must be defined in monetary terms. Since this type of valuation is challenging for both methodological and ethical reasons, formal cost-benefit analysis is not common in the medical literature.

Cost-effectiveness analysis

Unlike cost analysis and cost-benefit analysis, which each have a single monetary outcome measure, cost-effectiveness analysis (CEA) examines two outcome measures: cost in monetary terms and effectiveness in years of life saved, quality-adjusted life years (QALYs) saved, or disability-adjusted life years averted. Different clinical interventions and strategies are compared and ranked in terms of their incremental cost-effectiveness ratio, which is defined as: $(C_A–C_B)/(E_A–E_B)$, where $C_A–C_B$ is the difference in the cost of the two interventions, A and B, and $E_A–E_B$ is the difference in effectiveness of the same two interventions. When quality of life (or patient 'utilities') is included in the effectiveness measure, the ratio is expressed in dollars per QALY saved; this is also known as a cost-utility analysis. These incremental cost-effectiveness ratios (ICERs) are a measure of value for money. The higher the cost-effectiveness ratio the less cost-effective the intervention, since it costs more resources to improve survival by one year or one QALY. By using agreed-upon conventions for this methodology [34], one can compare the cost-effectiveness of different health interventions within a given clinical setting or country. How one defines exactly what might be considered 'cost-effective' is a matter of debate, although in the United States interventions that cost <$100,000/QALY gained are often considered cost-effective [35]. In the international setting, while there is no clear consensus, policy-makers often discuss cost-effectiveness ratios in the context of a country's annual per capita gross domestic product (GDP) where ICERs below three times this sum might be considered 'cost-effective' and those below it, 'very cost-effective'.

Modelling and cost-effectiveness in HIV disease and treatment

From the earliest days of the HIV epidemic, mathematical modelling and cost-effectiveness analysis have played an important role. The initial focus was on prophylaxis and treatment of opportunistic infections, including *Pneumocystis jirovecii* pneumonia (PCP), *Mycobacterium avium* complex, CMV and others

[36–38]. With the advent of effective ART in the mid-1990s, at a cost of ~$20,000/person/year in the US, there was a marked increase in the development and use of cost-effectiveness analysis in the US and in Europe [39–41]. Model-based studies highlighted that, even at these ART costs, HIV treatment provided excellent value (~$23,000/QALY saved, and well below accepted cost-effectiveness thresholds in the US) compared with other routine medical interventions, such as coronary artery bypass surgery and cancer screening [40].

The development of the Global Fund for AIDS, TB and Malaria, as well as the US President's Emergency Plan for AIDS Relief (PEPFAR) along with international pressure, led to a striking decrease in ART costs and increase in ART availability in resource-limited settings [42–44]. In this context, model-based cost-effectiveness analyses highlighted the value of ART in even the poorest of countries, including South Africa, Côte d'Ivoire, Zambia and others, with reference to their own GDPs [45–47]. These cost-effectiveness analyses of HIV treatment have been incorporated into national guidelines in the United States, France, Brazil, Chile, Mexico, and other countries, as well as those of the World Health Organization [48–53].

Mathematical modelling and cost-effectiveness analysis in advance of and alongside HIV cure trials

While laboratory and clinical studies are needed to assess both the efficacy and toxicity of HIV cure strategies, it will not be possible with these studies to assess all of the clinical parameters relevant to cure, including the potential for toxicities and relapse, which occur after the end of any trial. The overall risks and benefits, as well as costs, cost savings and cost-effectiveness associated with any HIV cure strategy will be impossible to capture in any single clinical trial [15]. Thus, by incorporating data from multiple studies into a modelling framework, and using uncertainty analysis, as described below, one can begin to assess the cost-effectiveness and policy implications of these strategies.

There are a number of important issues to consider with regard to the benefits of modelling HIV cure (Table 1). Current cure studies generally focus on patients with early HIV infection, although these patients are challenging to identify and represent a very small minority of all infected patients. In that context, models can simulate a variety of target populations for cure interventions, including those recently infected and untreated, chronically infected and untreated, or on effective ART, as well as those with different nadir CD4+ T cell counts or CD4:CD8 ratios. Each of these types of patients may have a different type of latent reservoir. Additionally, models can be used to evaluate the potential transmission benefits of cure compared to lifelong ART; either might be associated with later undiagnosed viral recrudescence and with increased risk of transmission. The relatively high-level viraemia immediately after viral recrudescence suggests that such failures could pose substantial public health risks, particularly if they occur long after the intervention at a time when close monitoring is no longer ongoing [54]. Moreover, modelling can be used to compare the outcomes of cure strategies to lifelong ART in various clinical scenarios. This will provide valuable insights because the costs of standard ART depend on the number and types of regimens available, the monitoring needed to assess the continued efficacy of these regimens, and the risk of developing both typical HIV-related conditions as well as other non-communicable diseases in the setting of HIV. These may differ substantially depending on the country or region of the world under consideration for cure interventions [55].

Another major benefit of simulation modelling approaches is that they can be used, in conjunction with early clinical data from selected trials, to assess the impacts on long-term outcomes with strategies that vary based on efficacy, early and late toxicity, relapse and cost. Data are now available about these parameters for ART in many settings, including those which are severely resource-constrained, suggesting that modelling analyses can be useful to determine the parameters of a cure strategy that might be feasible, cost-effective and affordable compared to ART [56]. Sax *et al*. evaluated the efficacy, toxicity, cost and relapse rate combinations that would make an HIV cure approach cost-effective in the US when compared to ART [57]. This model-based analysis found that a gene therapy-type approach would be cost-effective, that is, representing good value for money, in the US at 10% efficacy and 0.5%/month relapse if it cost $50,000/person for a one-time treatment, or with 50% efficacy and 0.5%/month relapse if it cost $200,000/person. It would be cost-saving at 40% efficacy, no relapse or fatal toxicity, and a one-time cost of $34,000/person. This study highlighted the efficacy and toxicity thresholds at which a given strategy might be acceptable from a policy perspective.

Mathematical modelling can also be a valuable tool in HIV cure research by projecting beyond the time horizon of clinical studies, simulating long-term outcomes of interventions based on available data on short-term outcomes that might be obtained in clinical trials, and evaluating more strategies than is possible in a single trial and/or in different stages of disease [58,59]. While any analysis of this type needs to address carefully the uncertainty of future events, modelling provides a framework within which the maximum amount of information may be derived from available sources. This includes data on the natural history of disease, as well as the most up-to-date information concerning the efficacy and toxicity of standard and newly designed interventions. Consequently, it is possible to compare the effectiveness and toxicity trade-offs for individual and/or combinations of cure interventions [34].

If models are to play a role in planning and evaluating HIV cure research, it is important to ensure that there are well-defined criteria for ensuring model transparency and quality [60]. This can be done by explicitness in model inputs, as well as structural considerations, through not only publications but through the availability of online technical appendices providing additional information [61]. Formal assessment of uncertainty in key variables through sensitivity analysis is also critical. These mechanisms can play an

Table 1. The role of mathematical modelling and cost-effectiveness analysis in HIV cure research

• Integrating multiple components of strategies: ○ Efficacy, toxicity, early and late relapse and cost
• Projecting long-term outcomes from short-term studies
• Evaluating more strategies than possible in a single clinical trial
• Assessing the impact in different target populations
• Evaluating the potential transmission benefits of cure
• Determining the cost-effectiveness, as well as affordability, of cure strategies compared to current antiretroviral therapy
• Assessing the Value of Information (VOI) to be gained from proposed large-scale trials

important role in providing increased confidence to decision-makers in model outcomes.

Value of Information analysis

Given the anticipated cost of clinical trials related to cure strategies, one key question that investigators will face, particularly with regard to promising strategies, is: 'How much should we be willing to pay for clinical trials to evaluate alternative cure strategies?' The anticipated cost of such trials – including the interventions, follow-up and laboratory-based confirmation of cure for each participant – would be substantial [62]. Value of Information (VOI) analysis is a novel, model-based approach to examine this exact question for trials of all types [63]. VOI is a forward-looking assessment aimed at determining whether to acquire new information through a trial, or trials, to inform the ability to make decisions about specific strategies. That is, would a trial be 'worth' doing, and what would be the clinical and economic value of the results? VOI formally compares the best courses of action, both with and without the additional information related to potential strategies for care and cure that would be obtained in a trial [64]. Recent VOI analyses have highlighted the importance of conducting randomised trials of intravenous immunoglobulin for severe sepsis, as well as the value of a definitive trial of lymph node dissection in endometrial cancer [65,66].

Acquisition of information through trials entails both 'costs' and 'benefits' (denominated in dollars, health outcomes, time or all of the above), and includes the clinical risks of a treatment or a trial-based intervention, the health impact of delayed decision-making, and the economic cost of inaction while awaiting trial results, in this case the cost of ART and other HIV treatment for those who might benefit from a cure strategy. VOI analysis also incorporates the later, or 'downstream' costs associated with the choice of whether to do a trial: how many people would be influenced by the results of such a trial? How would the costs of care for those people, over a specified time horizon, change with and without the trial results? All of these factors are incorporated into the structure of VOI analysis to fully inform planners' goals for and value of the clinical trial under consideration.

Summary

With the global HIV pandemic now in its fourth decade, evidence suggesting the real possibility of HIV cure is accumulating. With a number of promising strategies in development and multiple clinical trials ongoing, modelling studies can highlight the potential cost-effectiveness of such interventions, as well as the economic value of information to be gained by undertaking clinical trials. Given the scope of the HIV pandemic, as well as its ongoing cost in both human and economic terms, studies aimed at characterising the clinical and economic implications of various cure strategies under investigation are an important priority.

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Declaration of interests

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