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Antiretroviral therapy for initial human immunodeficiency virus/AIDS treatment: critical appraisal of the evidence from over 100 randomized trials and 400 systematic reviews and meta-analyses

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Abstract

There have been over 100 randomized clinical trials (RCTs) of diverse regimens of antiretroviral therapy for treatment-naïve human immunodeficiency virus-positive patients. A further 400 systematic reviews and meta-analyses are informed by these trials. There are, however, difficulties in using systematic reviews and meta-analyses of this clinical evidence to inform guidelines and clinical practice. Several issues can make the interpretation of comparative effectiveness challenging. In this article, we review the key challenges in interpreting multiple trials in this population. We specifically examine the network geometry of the clinical trial comparisons, the predominance of non-inferiority trial designs, issues related to potential class effects, heterogeneous documentation of adverse events, and a relative lack of RCTs that reflect specific current clinical guideline recommendations. We conclude with recommendations for future clinical trials and meta-analyses.

Keywords: Adverse events, antiretroviral therapy, class effects, HIV/AIDS, meta-analysis, network meta-analysis, non-inferiority, randomized clinical trials, systematic reviews

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Introduction

Antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection has revolutionized how HIV is treated and how care is provided to populations around the world [1]. The documentation of survival benefits from combination triple therapy ART in 1996 led to a downturn in mortality from HIV infection worldwide [2]. Subsequently, the President's Emergency Plan for AIDS Relief (PEPFAR) in 2003 marked the largest roll-out of a drug-based intervention around the world [3]. Because ART reduces the amount of virus in compartments relevant for transmission, such as blood, semen, and the genital tract [4], and can therefore reduce transmission of the virus [5], many political and scientific leaders are now postulating the prospect of an AIDS-free generation [6].

There are now 28 antiretroviral drugs on the market, and these are typically classified according to their drug class. The six primary drug classes are: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); integrase inhibitors (IIs); and entry inhibitors (CCR5 agents and fusion inhibitors). Antiretroviral agents are available individually or as fixed-dose combinations, i.e. multiple antiretroviral drugs within a single pill. ART can vary from multiple individual drugs taken multiple times a day to a single, once-daily pill. More than 9 000 000 people are now receiving ART, and the yearly price of ART varies from $300 (and decreasing) per person in PEPFAR programmes to more than $24 000 in the USA, depending on the choice of drug [1,7].

Since 1996, several ART drugs have come and gone (e.g. zalcitabine and standard-dose ritonavir) in clinical practice. The reasons why drugs may become unfavoured are heterogeneous, but include unfavourable risk profiles, poor levels of viral suppression, unfavourable resistance profiles, and complex dosing schedules. For example, zalcitabine, of the NRTI class, was discontinued in 2006 because of its frequent serious adverse events, including peripheral neuropathy in up to 34% of patients [8], and the inconvenience of needing to be ingested every 8 h. As newer ART drugs have not had the benefit of time to evaluate them, it seems likely that several of the newer agents will also be set aside as we develop a better understanding of their clinical profile and tolerability.

Given the widespread use of ART and the important individual and public health implications of its use, we should expect that the available clinical trial evidence supporting their use and informing guidelines would be robust. WHO, International AIDS Society (IAS), US Department of Health and Human Services and European AIDS Society guidelines are carefully revised on a frequent basis, and may influence the clinical treatment of millions of patients. However, even more successes could be achieved if the clinical trials conducted in this field built on the already accumulated clinical evidence and avoided pitfalls. In an initial search of the published literature on randomized clinical trials (RCTs) of ART for ART-naïve adult patients, we identified 98 RCTs published as full-text articles since 2002, the turning point when ART began to become widely available in low-income and middle-income countries (details of the search strategy and screening process are available from the authors). Fig. 1 shows the numbers of RCTs and systematic reviews (with or without the inclusion of meta-analyses) published per year. These trials have informed >400 systematic reviews (many of them also including formal meta-analyses) over this period. This initially looks like an impressive amount of clinical evidence for one specific condition. However, upon closer inspection, the accumulated evidence leaves much to be desired, as addressed in this review.

Currently, sales of these drugs are led primarily by guideline endorsements, and, perhaps less than in other fields, by marketing to physicians and directly to patients. HIV/AIDS, more than any other field, has had a strong advocacy alliance of patient groups and representatives demanding access to drugs and advocating for early approvals and reduced prices. Such advocacy has successfully reduced the price of treatment for an average patient in Africa (including laboratory support), for example, from *c.* $10 000 per year in 2002 to *c.* $300 per year or less in PEPFAR programmes [7]. Perhaps, if the same level of advocacy can now be applied to the conduct and sharing of clinical trial data, the evidence needed to safely and effectively

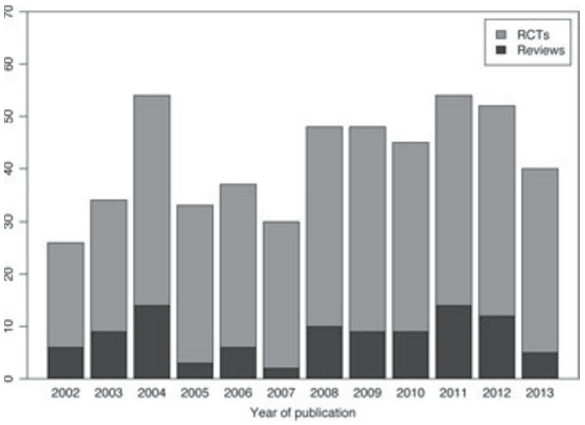

FIG. 1. The number of randomized clinical trial (RCT) and systematic review/meta-analysis publications pertaining to antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) treatment-naïve adults. We searched ten electronic databases (MEDLINE via PubMed, Cochrane CENTRAL, EMBASE, CINAHL, AMED, PsychINFO, Clincaltrials.gov, HIV drug resistance database, Global Health, and Web of Science) for randomized trials of individual ART by using the search terms 'MESH agents, antiretroviral', 'MESH HIV', 'MESH Acquired immunodeficiency syndrome', 'random*', and 'naïve or initial or early'. We searched for systematic reviews by using the same search terms with the addition of 'systematic review OR meta-analysis', and used the Pubmed Clinical Query search filter for systematic reviews.

treat long-term HIV infection may allow much improved outcomes for patients.

Patients, clinicians and regulators want different types of evidence to make decisions. Patients and clinicians want to know which regimen is most effective and most safe for each individual having to undergo life-long treatment; regulators such as the US Food and Drug Administration and the European Medicines Agency want to ensure that treatment effects are well documented; and the pharmaceutical industry wants to provide the best return for its investors. Each group vigorously argues for its interests, and, ultimately, each group must compromise to a certain extent. Ostensibly, such strong advocacy by the groups means that they keep each other accountable. However, strongly held views have, at times, prevented access to effective treatments. When the large conglomerate of pharmaceutical companies refused to reduce drug prices in Africa in 2000, patient and clinical groups took legal action to ensure access to drug treatments in South Africa [9]. The pharmaceutical industry quickly realized that addressing patient and physician needs would become a necessary component of future business. If the field of HIV/AIDS care is to advance rapidly, relevant clinical trials that