The contribution of observational studies in supporting the WHO 'treat all' recommendation for HIV/AIDS

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Abstract

In 2015, the World Health Organization (WHO) recommended that all people living with HIV (PLWH) should start antiretroviral therapy (ART) irrespective of clinical or immune status. This recommendation followed almost 20 years of research into the clinical and population-level benefits and risks of starting ART early compared with deferring treatment. This article summarises the ways in which observational data support the work of WHO, including the support provided by the International epidemiology Databases to Evaluate AIDS (IeDEA), taking the example of 'treat all'.

Introduction

In 2015, the World Health Organization (WHO) recommended that all people living with HIV (PLWH) should start antiretroviral therapy (ART) irrespective of clinical or immune status [1]. This recommendation followed almost 20 years of research into the clinical and population-level benefits and risks of starting ART early compared with deferring treatment [2].

The WHO 'treat all' recommendation was supported by evidence from randomised trials showing significant clinical benefits and a reduced risk of HIV transmission following immediate ART initiation [3-5]. The randomised trials confirmed an association that was reported by prior observational studies [6-9]; however, observational data alone were insufficient for the WHO guidelines panel to make a 'treat all' recommendation when this question was first assessed in 2013. Nevertheless, the observational evidence helped to strengthen the rationale for this recommendation. Observational studies have also provided important additional evidence supporting the feasibility of implementing the 'treat all' approach, and these studies continue to generate insights into the challenges and benefits of a treat-all policy across different settings and populations.

This article summarises the ways in which observational data support the work of WHO, including the support provided by the International epidemiology Databases to Evaluate AIDS (IeDEA) [10], taking the example of 'treat all' (see Table 1).

Role of observational data in WHO guidelines

The development of high-quality guidelines relies on a systematic review of the evidence and an appraisal of the certainty of the evidence. Guideline development processes have widely adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [16], which, following a long-standing approach to ranking evidence [17], rates randomised trials as generally providing high-quality evidence for questions of intervention effect, and observational studies as providing low-quality evidence (in certain exceptional situations observational studies can be considered to provide evidence of high quality [18]).

WHO adopted the GRADE approach in 2008, following public criticism that many WHO guidelines at the time relied too heavily or exclusively on expert opinion [19]. In contrast to clinical practice guidelines, WHO guidelines aim to make recommendations from a public health perspective, and are thus primarily intended for ministries of health and programme managers in low- and middle-income settings, rather than individual clinicians. As such, the formulation of WHO recommendations relies not only on information about comparative effectiveness and harms, but also considerations about the feasibility, acceptability and resource requirements for implementing a given intervention or set of interventions as well as complex interventions. While randomised trials remain the gold standard study design for assessing efficacy and safety of clinical interventions, observational studies are often a better way – and in some cases the only way – to assess intervention effectiveness in routine settings.

WHO also has a responsibility to evaluate the uptake and impact of the recommendations it makes, and these evaluations rely on observational research from implementation in routine programmes. Lessons from these studies serve to highlight challenges in implementation, which in turn can inform priorities for future guidance (Figure 1).

From treating the sickest to 'treat all': formulating recommendations

WHO first considered making a recommendation to start ART in all people living with HIV irrespective of clinical or immune status in 2013. At the time, there were no available data from randomised trials with respect to clinical benefit, and guideline deliberations were primarily informed by observational data and mathematical modelling. The 2013 WHO Guideline Development Group concluded that there was insufficient evidence to recommend 'treat all', and WHO instead recommended that the CD4 cell count threshold for stating ART be raised from ≤350 cells/mm^3 to ≤500 cells/mm^3 [20].

Randomised controlled trial evidence was available demonstrating the benefit of providing immediate treatment in the context of serodiscordant partnerships to reduce HIV transmission [5], and this recommendation was included in the WHO 2013 guidelines.

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source: https://doi.org/10.7892/boris.122500 | downloaded: 12.10.2024

Table 1. Analysis of data from the International epidemiology Databases to Evaluate AIDS (IeDEA) to inform WHO guidelines

Guideline	Evidence contributed	Analyses performed
WHO 2010 ART guidelines for HIV infection in infants and children	Definition of immunological failure in children on ART	Risk of mortality associated with different ages and CD4 values in children on ART [11]
WHO 2013 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection	Support for ART for all children aged <5 years irrespective of disease severity	Causal modelling of observational data comparing mortality with immediate versus deferred ART in children aged 1–5 years [12]
WHO 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection	Support for ART for all children aged <15 years irrespective of disease severity	Causal modelling of observational data comparing mortality and growth with immediate versus deferred ART in children aged 1–15 [13]
WHO 2017 guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy	Definition of burden of advanced HIV disease in adults and children	Proportion of adults in IeDEA and COHERE collaborations presenting with advanced HIV disease; proportion of children aged<5 years in IeDEA-SA presenting with advanced HIV disease [14,15]

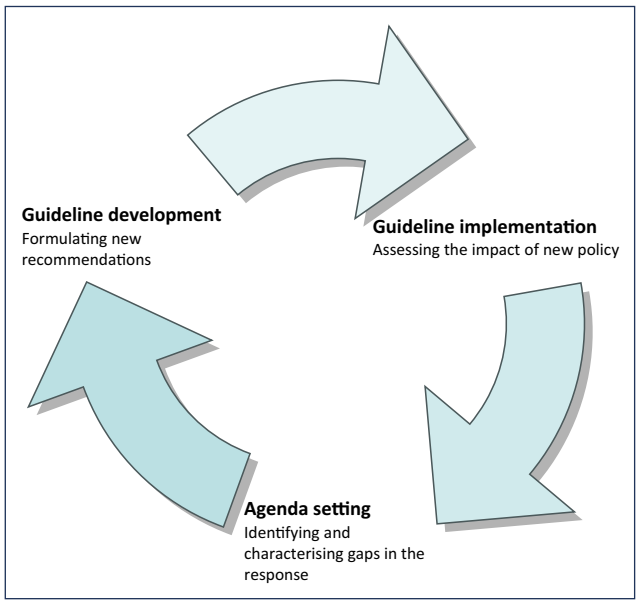

Figure 1. The contribution of observational data to guideline development at WHO

For pregnant women with HIV, a recommendation was made in favour of starting ART irrespective of CD4 cell count (PMTCT Option B+) [21]. This recommendation, aimed at increasing ART uptake among pregnant women, was based on a recognition of the need to simplify ART provision during pregnancy and breastfeeding, and to avoid delays in starting ART in pregnant women in settings where CD4 cell count testing was not available or where waiting for results could result in missed opportunities to prevent vertical transmission. Evidence supporting the benefits of this approach came from observational studies that provided outcomes from programmes implementing Option B+; these studies all found that uptake of ART was more timely, and that women experienced health benefits in terms of immunological and clinical parameters [22–24].

Similarly, ART initiation for all children aged under 5 years was recommended to address the low treatment coverage in children; however, at the time, this recommendation was made in the absence of randomised controlled trial evidence of clinical benefit, and primarily on the basis of observed rapid immunological decline in the absence of ART as well as causal modelling analysis of observational data from Southern Africa [13].

While several observational studies also suggested a clinical benefit to providing lifelong ART as soon as possible following an HIV diagnosis [9,25], the WHO recommendation was only made 2 years later, once data from the START and TEMPRANO randomised trials became available [3,4]. However, these trials did not include children, and the 'treat all' recommendation across all age groups, including children, was supported by observational data (17 cohort studies) and mathematical modelling [26,27] (Table 1).

The WHO recommendation to treat all people living with HIV also raised questions regarding how quickly ART should be initiated following confirmation of HIV diagnosis. Removing the need to have the results of clinical or laboratory assessments on hand prior to starting ART opens up the possibility to start ART on the same day that an HIV diagnosis is confirmed. In 2017, WHO recommended that ART should be offered within 7 days following a confirmed HIV diagnosis, including the offer of initiating ART on the same day as diagnosis [28]; this recommendation was informed by data from four randomised trials and 11 observational studies [29].

Benefits and challenges of 'treat all': assessing implementation

The clinical benefits of 'treat all' are no longer disputed, and this recommendation has been adopted by almost all countries worldwide [30]. Questions remain, however, regarding the feasibility of implementation and the extent to which the benefits seen in clinical trials will be realised in routine programme settings [31].

Drawing on both IeDEA data and information retrospectively gathered on the nature and timing of country-specific ART guideline expansion, a recently published analysis from the IeDEA–WHO Collaboration [32] found that ART guideline expansion supporting earlier ART initiation is associated with increased and more timely uptake of ART [33]. This analysis further showed that these improvements did not come at the expense of crowding out sicker patients. This analysis has recently been updated to include settings that have implemented 'treat all' and concluded that the greatest improvements in timeliness of ART initiation under successive guideline expansions that included expansion to 'treat all' occurred in low-income countries, likely to be due to the simplification of initiation decisions, i.e. opening the possibility to initiate treatment while waiting for baseline CD4 cell count test results. Young people aged 15–25 years also benefited from more timely ART initiation under 'treat all', as CD4 cell count-based guidelines disadvantaged this group of patients, who were likely to have been recently infected and therefore more likely to have higher CD4 cell counts.

Experience of implementing 'treat all' for pregnant and breastfeeding women (Option B+) has found that, while the approach is feasible across a variety of settings, there is a need to ensure

adequate retention in care and medication adherence, particularly during the first year following ART initiation [34]. This may also be a concern for anyone starting ART at higher CD4 cell counts, although the evidence so far is mixed [35,36].

Implementation of recommendations for rapid ART initiation has also been informed by observational data. While the results of several randomised trials all favoured rapid ART initiation, in particular by reducing the risk of loss to follow-up before ART initiation, some observational studies reported increased losses to follow-up after ART initiation. This suggests that different approaches to adherence counselling after starting ART may be needed when ART is started rapidly, as people are still coming to terms with their diagnosis. A recent study by the IeDEA collaboration in Rwanda suggested that patients enrolling in care at sites conducting fewer ART readiness counselling sessions initiated ART more rapidly and had better retention 6 months post initiation [37].

Identifying gaps in policy and practice

Observational cohorts provide valuable insights into the programmatic impact of ART scale-up and, in doing so, can reveal gaps in the response that are a priority for future intervention research and policy guidance.

Several studies from the IeDEA collaboration have highlighted the fact that men with HIV have worse outcomes compared to women with HIV [38,39], and this has contributed to a recognition of the need to identify models of care to improve uptake and outcomes for men [40].

The enduring burden of advanced HIV disease is another challenge that has been highlighted through observational research. Successive studies by the IeDEA collaboration have shown that, despite major progress in ART scale-up, an important proportion of patients continues to present late for care, with advanced HIV disease [14,41,42]. This work directly contributed to the development of WHO guidance on the management of advanced HIV disease in 2017 [28], and continues to drive discussions about how to best promote earlier diagnosis and linkage to care globally.

Rapid introduction of new antiretrovirals for which limited experience has been gathered outside the setting of randomised clinical trials requires increasing attention to longer-term monitoring of treatment outcomes and toxicity profiles across populations. As countries strengthen their pharmaco-vigilance systems to enable active monitoring and high-quality surveillance, cohort collaborations such as IeDEA can play a critical role in addressing this important evidence gap.

Future research will improve our understanding of the challenges faced in implementing the 'treat all' policy, in particular whether there are differences in adherence, retention, viral suppression and viral resistance among people starting ART without having developed clinical disease, and the possible need for differential adherence support for different patient populations. Indeed, observational research has the advantage of capturing the experience and patient outcomes that occur outside the controlled environments of research protocols and are critical for policies and guidelines, including large populations of persons who are not typically recruited into, or represented, in randomised trials, but are none the less differentially impacted by the HIV epidemic, such as children, pregnant women, persons with TB, persons with mental health and substance use disorders, and marginalised populations. Observational cohorts, such as IeDEA, also have the advantage of scale and the ability to examine implementation and health outcomes in a variety of diverse settings and care delivery contexts.

Conclusions

Evidence from observational cohorts has made a central contribution to the development of WHO guidelines, and will continue to do so. Observational data can be especially critical for groups of people who have not been enrolled in randomised trials in addressing a given implementation question, for example, pregnant women and children. Randomised trials are also not generally well suited for assessing rare harms (owing to limited sample sizes and rigorous exclusion criteria), which often only become apparent when a drug is being rolled out. In addition, observational studies provide valuable insights into the feasibility and implementation challenges associated with a given intervention or set of interventions. Finally, increasing attention is being paid to the need to evaluate the uptake and impact of WHO guidelines on critical health outcomes in countries (Figure 1). Observational studies are well suited to evaluating the impact of policy change in routine practice.

The continued contribution of observational data to shaping the response to HIV depends on continued investment in data systems by national programmes and international donors. It has been recommended that 5–10% of all HIV programme budgets be directed towards data collection and use [43]. Sustained investment in the generation and analysis of observational data will make an important contribution to programme performance, as well as helping to inform the global response.

Approaches to data interpretation are being continuously updated to improve the reliability of evidence from observational research. Collaboration between cohorts across different countries can enhance the comparability of findings and their generalisability (provided all findings point in the same direction) or point towards important sources of heterogeneity (if they do not). Advances in statistical software have increased the usage of tools such as multiple imputation to analyse incomplete datasets. Increased use of design and analytical approaches, such as regression discontinuity, difference-in-difference, g-estimation and propensity score have helped achieve more analytical rigour for assessing causal associations and impact, provided the most critical confounders have been directly or indirectly controlled.

The IeDEA–WHO partnership [32] is an example of an effective collaboration that can provide valuable insights into whether WHO guidelines are making a difference to outcomes for people living with HIV, and guide how future IeDEA analyses can have more policy relevance. The potential to expand this collaboration to cover other disease areas should be explored.

Acknowledgments

Funding

The International Epidemiology Databases to Evaluate AIDS (IeDEA) is supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, and the National Institute on Drug Abuse: Asia-Pacific, U01AI069907; CCASAnet, U01AI069923; Central Africa, U01AI096299; East Africa, U01AI069911; NA-ACCORD, U01AI069918; *Southern Africa*, U01AI069924; West Africa, U01AI069919. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

Acknowledgements

Conflicts of interest

The authors declare no conflicts of interests.

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