Antiretroviral resistance testing in treatment-naïve people living with HIV (Protocol)

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[Intervention Protocol]

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness of antiretroviral resistance testing (genotypic, phenotypic, or virtual phenotypic) in reducing morbidity and mortality in treatment-naive people living with HIV

BACKGROUND

Description of the condition

Close to 35 million people are living with human immunodeficiency virus (HIV) worldwide (UNAIDS 2014). They are living longer and healthier lives thanks to the use of antiretroviral therapy (ART), which reduces the mortality and morbidity associated with HIV infection. Even though only 34% of those eligible for ART are currently receiving it, efforts are underway to improve access to ART (UNAIDS 2013). Effective ART inhibits viral replication and reduces viral load. The World Health Organisation (WHO) Model List of Essential Medicines contains a list of antiretroviral drugs grouped into three classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PIs; WHO 2013). Recommendations on how they should be used include considerations of cost, availability, ease of administration, efficacy, toxicity and potency. The potency of these medications is severely compromised in the presence of drug resistance. In addition, the combination of drugs should be chosen with care, given that in some classes of antiretroviral drugs (NNRTI) cross resistance is possible - any mutation for one drug will lead to resistance in all the other drugs in the class (Deeks 2001).

Many problems abide in HIV care including limited access to ART in some parts of the world, sub-optimal levels of adherence and the development of resistant viral strains (UNAIDS 2014). International commitment to a unified response to the HIV pandemic is improving access to ART, and numerous research efforts attempt to pin-point the best adherence enhancement strategies (Chaiyachati 2014; Thompson 2012; Mills 2006; Nachega 2012; Ramjan 2014). However, viral resistance to ART is a growing problem in people living with HIV. Resistance can either result from the acquisition of mutant strains of the virus or from their selection

within the individual (from inappropriate use: poor adherence in terms of dosing and timing; and treatment interruptions).
For people living with HIV and taking ART, the emergence of drug resistance poses a serious threat to a sustained virologic response to treatment, it reduces effective therapeutic options, and would increase morbidity, mortality and infectivity. All the above would lead to increased health care costs for individuals and society. Drug resistance may be transmitted (transmitted drug resistance; TDR) or acquired (drug resistance mutation; DRM; Rojas 2014).
There is increasing evidence of antiretroviral resistance in treatment-naive individuals (Duwe 2001; Torti 2004; Bakhouch 2009; Barrow 2013; Rojas 2014). This resistance would most likely be TDR in newly-infected individuals. Even though TDR may be stabilizing in high income countries, it is on the rise in low income countries (Pham 2014).

Description of the intervention

Antiretroviral resistance testing may be done in one of two ways: **genotypic testing** involves direct examination of the genetic material of the virus to determine which medications it is resistant to; and **phenotypic testing**, which measures the effects of medication on the virus in a controlled environment. Both methods require at least a week for results to be obtained, genotypic testing is cheaper, but phenotypic testing is easier for care providers to interpret. These tests provide information on the three main classes of ART (AIDS INFO 2014).

How the intervention might work

Currently, the WHO recommends population based surveys to measure levels of drug resistance (WHO 2014), yet it is unclear what levels of resistance call for action and exactly what action should be taken (Cambiano 2013). Data from such surveys in resource-limited settings suggests that at 12 months, two-thirds of those who do not achieve viral suppression on first line therapy may have drug resistance (Hosseinipour 2013). Viral resistance in treatment-naive persons can potentially compromise virologic response even before ART initiation, suggesting the need for HIV resistance testing before ART initiation (Barennes 2014). Drug-resistance testing is therefore necessary and currently recommended to guide the choice of the therapeutic regimen in treatment-experienced and treatment naive individuals (Durant 1999; Baxter 2000; Cingolani 2002; Meynard 2002; Tural 2002; Hirsch 2008). If pre-ART resistance testing of treatment-naive people with HIV shows evidence of resistance, then it might be necessary to carry out routine resistance testing prior to ART initiation in order to guide therapeutic choices and potentially reduce the advent of virologic failure.

Why it is important to do this review

The European HIV Drug Resistance Guidelines Panel (Vandamme 2011) and International Antiviral Society-USA Panel (Gunthard 2014) both recommend resistance testing prior to initiation of ART, yet the WHO does not. The WHO recommend a survey-based method to detect population level development of resistance (Bennett 2008). This review will use data from randomized trials to highlight the benefits or harms of conducting resistance testing in individuals prior to initiation of ART and may provide information for economic evaluations.

OBJECTIVES

To evaluate the effectiveness of antiretroviral resistance testing (genotypic, phenotypic, or virtual phenotypic) in reducing morbidity and mortality in treatment-naive people living with HIV

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that evaluate the clinical and biological outcomes in treatment naive people with HIV who undergo resistance testing compared to no resistance testing

Types of participants

Treatment-naive HIV-positive individuals of any age

Types of interventions

Any type of resistance testing in treatment-naive HIV-infected adults prior to initiation of therapy. Genotypic and phenotypic tests will be included. Studies that compare different methods of resistance testing against each will not be included.

Types of outcome measures

Primary outcome measures

- Mortality (proportion of deaths)
- Virological success. The proportion of participants achieving undetectable viral load (using lower limits for detection and time frames defined by the authors).

Secondary outcome measures

- Change in mean CD4-T-lymphocyte count (immunologic response) over time.
- Clinical progression to AIDS: The proportion of participants that develop CDC-defined AIDS (stages III and IV)
- Development of a second or new opportunistic infection.
- Quality of life (as reported by the authors).

Search methods for identification of studies

Our search will be conducted with the assistance of the HIV/AIDS Review Group Trials Search Coordinator. A comprehensive and exhaustive search strategy will be adopted to identify studies in all languages irrespective of publication status (published, unpublished, in press or in progress). Searches will be conducted from 1989, the year in which the first case of antiretroviral drug resistance was identified

In addition to key antiretroviral terms used in the Cochrane HIV/AIDS Group's standard search strategies, we will include all appropriate terms relevant to antiretroviral resistance testing, including Medical Subject Heading (MeSH) terms. We will also use Cochrane Collaboration's Highly Sensitive Strategy for identifying reports of RCTs.

Electronic searches

The following electronic databases will be searched for relevant randomized controlled trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (1 January 1989 to search date)
2. PubMed (1 January 1989 to search date)
3. EMBASE (1 January 1989 to search date)
4. CINAHL (1 January 1989 to search date).
5. Latin American and Caribbean Health Sciences Literature (LILACS) (1 January 1989 to search date)
6. Web of Science (1 January 1989 to search date)

Conference abstracts:

We will search conference abstract archives on the web sites of the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS), for all available abstracts presented at all conferences from 1989 through 2014.

Ongoing trials:

- The WHO International Clinical Trials Registry Platform
- ClinicalTrials.gov

Searching other resources

The reference lists of pertinent studies will be searched for more titles.

Data collection and analysis

A summary of the identification, screening and inclusion of studies in this review will be presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram (Moher 2010).

Selection of studies

Two reviewers (LM and JT) will independently inspect the titles and abstracts of each reference identified by the search for relevance.Full text copies of all the relevant titles will be downloaded and screened. Only those that fulfil our inclusion criteria will be included. Disagreements will be resolved by consensus. When a consensus can't be reached a third author will be contacted for adjudication.

Data extraction and management

Pilot tested data abstraction forms will be used to extract data from the included studies.Two reviewers (LM and JT) will independently extract the data of included trials. In case of any disagreement between the two reviewers, a third independent reviewer will adjudicate. When necessary (missing information or unclear reports), the authors of the trials will be contacted for clarification. For reports not published in English, other scientists with Cochrane methods expertise will be invited to assist with screening and data extraction. We will collect bibliometric information, data on the participants, interventions, comparisons, outcomes and study duration.

Assessment of risk of bias in included studies

The risk of bias will be assessed using the following.

- Sequence generation: how the allocation sequence was generated and whether it was adequate.
- Allocation concealment: how the allocation sequence was concealed and whether it was adequate.
- Blinding of participants, personnel, and outcome assessors.
- The description of the completeness of outcome data for each main outcome.
- Selective outcome reporting.
- Baseline characteristics for observational studies.
- Other potential sources of bias (e.g. funding).

Studies will be graded as being at high, low, or moderate risk of bias. 'Risk of bias' tables will be filled independently by the two authors.

Measures of treatment effect

Datawill be analysed using Review Manager (Revman 2014). GradePro (Grade Pro 2014) software will be used to produce Summary of Findings tables. We will calculate the risk ratio (RR) or

the odds ratio (OR) for binary data, the weighted mean difference (WMD) for continuous data measured on the same scale, and the standard mean difference (SMD) for continuous data measured on different scales. These results will be presented with 95% confidence intervals (CI).

Dealing with missing data

For missing or unclear data, the authors of the studies will be contacted during eligibility assessment and data abstraction. Missing data may also be sought from secondary publications of the same study.

Assessment of heterogeneity

Studies will first be assessed for clinical heterogeneity. If studies are similar enough to combine (with regards to the participants, interventions, comparisons and outcomes), a meta-analysis will be performed and statistical heterogeneity assessed. Statistical heterogeneity will be assessed using the Chi^2 test for homogeneity with a level of significance, alpha = 0.10 and the I^2 statistic to quantify inconsistency.

Assessment of reporting biases

Reporting bias (selective outcome reporting) will be assessed using the Cochrane Collaboration Risk of bias tool. Publication bias will be assessed by using a funnel plot if we include ten or more studies (Higgins 2009).

Data synthesis

A fixed-effect meta-analysis will be performed to synthesize sufficiently similar quantitative data. Results from the included studies will be pooled to determine the OR and RR for the two compared interventions of achieving lower mortality and virological success.

Subgroup analysis and investigation of heterogeneity

The Chi^2 test of homogeneity will be performed to ensure that the differences between the results of each trial could not be expected by chance. If there is significant unexplained statistical heterogeneity a random-effects model will be used. Possible sources of heterogeneity in this review might include the potency of antiretroviral therapy used, the kind of resistance testing used and the level of advancement of disease. We hypothesize that studies, with more potent ART, more sophisticated resistance testing techniques and with patients at early stages of the disease will have better outcomes.

Sensitivity analysis

A sensitivity analysis will be performed to evaluate bias introduced by variability in study design and risk of bias.

ACKNOWLEDGEMENTS

This protocol was developed as part of the mentoring requirements for the Aubrey Sheiham Evidence-based Health Care in Africa Leadership Award. LM is mentoring JT.

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* *Indicates the major publication for the study*

WHAT'S NEW

Last assessed as up-to-date: 7 January 2015.

Date	Event	Description
7 January 2015	New citation required and major changes	New citation. New authors taking on this review.

HISTORY

Protocol first published: Issue 2, 2007

Date	Event	Description
7 January 2015	Feedback has been incorporated	Edits approved
6 January 2015	Amended	A few small edits.
5 November 2014	Amended	The protocol has been revised and updated

CONTRIBUTIONS OF AUTHORS

JT and LM jointly developed the first draft of the protocol and on several revisions.

DECLARATIONS OF INTEREST

None.

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Internal sources

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