Treatment outcomes for patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis[1]

OBJECTIVE

The objective of this study is to undertake a systematic review and meta-analysis of studies reporting proportions of patients experiencing virological failure on second line antiretroviral therapy

METHODS

Search Strategy

1. Search **(((((((hiv infections) OR HIV) OR human immunodeficiency virus) OR hiv virus) OR acquired immune deficiency syndrome) OR HIV-1) OR HIV seropositivity) OR HIV-2**

2. Search **((((("Anti-HIV Agents"[Mesh])) OR (("Antiretroviral Therapy, Highly Active"[Mesh])) OR "Anti-Retroviral Agents"[Mesh]) OR antiretrovirals) OR HIV treatment**

3. Search **(#1) AND #2**

4. Search **(((((((("HIV Protease Inhibitors"[Mesh]) OR second-line therapy) OR second-line treatment) OR lopinavir) OR ritonavir) OR atazanavir) OR indinavir) OR darunavir) OR saquinavir) OR (ritonavir AND lopinavir)**

[1] Contact: Nathan.ford@msf.org

5. Search **(#3) AND #4**

6. Search **((("Treatment Failure"[Mesh]) OR antiretroviral failure) OR second-line failure) OR first-line failure**

7. Search **(#5) AND #6**

8. Search **(#5) AND #6** Limits: **Humans**

Databases

- Cochrane Library
- PubMed
- EMBASE
- Central
- CROI (http://www.retroconference.org/)
- AEGIS (http://www.aegis.com/)
- IAS (http://www.iasociety.org/AbstractSearch.aspx)

Inclusion criteria

Types of studies

- Cohort studies
- Case series >10 patients

Types of participants

Inclusions:

- Treatment naïve HIV infected adults and children on PI containing second line antiretroviral therapy in resource-limited settings according to the World Bank classification
- Data will be disaggregated by age at analysis

Exclusions:

- Cohorts of exclusively failing patients

Types of interventions

- Mono or boosted PI-based second line antiretroviral therapy

Types of outcomes

Primary

- Proportion of patients with virological failure, according to definitions used by each study
- Sensitivity analysis will compare outcomes of studies that used WHO definition or not
- Occurrence of adherence-related virological failures
- Occurrence of virological failures due to resistance mutation to drug regimens

Secondary

- Mortality rates of patients on second-line antiretroviral therapy
- Rates of loss to follow up to second-line antiretroviral therapy

Data coding

Two authors (OA and SM) will independently screen titles and abstracts identified from the search by our eligibility criteria. Full text will be obtained for potential studies that meet eligible criteria and screened even further with the inclusion and exclusion criteria. Data from each study will be extracted into a standardized data extraction form in Microsoft Excel, coded with the following information: name of reviewer, author, title, year, publication status, study design, study location, age of study participants, type of analysis (ITT or As-treated), sample size, type of second-line drugs, treatment failure definition, follow-up duration for first-line therapy, follow-up duration on second-line therapy, pre-second-line baseline CD4, pre-second-line baseline viral load, baseline genotyping (Y/N), treatment failure outcomes, genetic mutation outcomes, adherence outcomes, mortality rate , lost-to-follow up rates, and other failure associated factors

Assessment of risk of bias

Two authors (OA and SM) will independently assess methodological quality of studies meeting our eligibility requirements by using a specially developed checklist that addresses

risk of bias across five different categories according to requirements by The Cochrane Handbook for Systematic Reviews. These categories include:

Selection bias:

- Were all patients PI-naïve at baseline?
- Were all eligible patients included in the study?
- Were patients with toxicities and abnormalities excluded from study?

Performance bias:

- Was the second-line regimen PI-based?
- Was there an objective criteria for defining treatment failure?
- Was viral load monitoring performed at baseline?
- Was genotyping performed at baseline?

Detection bias:

- Was adherence taking into account?
- Were all patients included in the analysis

Attrition bias:

- Was a follow-up time of at least 6 months of second-line therapy adhered to?

Reporting bias:

- Was selective reporting of any kind observed?

DATA ANALYSIS

Prevalence estimates

Point estimates and 95% confidence intervals (95% CI) will be calculated for the proportion of patients virologically failing second-line therapy. The variance of the raw proportions will be stabilised using a Freeman-Tukey type arcsine square-root transformation and estimates pooled using a DerSimonian-Laird random effects model.

Meta-analysis

Proportions will be pooled using the DerSimonian-Laird random effects method. The τ^2 statistic will be calculated to assess the proportion of overall variation attributable to between-study heterogeneity as this is less affected by the number of studies than the more commonly used I^2 statistic. Subgroup analyses will be conducted to assess the potential effect of patient and programme covariates. A p-value less than 0.05 will be considered to be significant.

Statistical software

Analyses will be conducted using Stata (version 11, www.stata.com).

Sensitivity analysis

We will conduct a sensitivity analysis to determine how the different definitions of treatment failure affect the results of the review.

Dealing with missing data

We will contact the first or corresponding author of each included study for missing data or complementary information.