

**Protocol for the systematic review of virological outcomes after 12 Months of antiretroviral therapy
in low and middle income countries**

1. Authors

James H. McMahon
Alfred Hospital, Melbourne, Australia
Tufts University School of Medicine, Boston, USA

Julian H Elliott
Alfred Hospital, Monash University, and Burnet Institute, Melbourne, Australia

Silvia Bertagnolio
World Health Organization, Geneva, Switzerland

Rachel Kubiak
Tufts University School of Medicine, Boston, USA

Michael R. Jordan
Tufts Medical Center and Tufts University School of Medicine, Boston, USA

2. Background

Resource barriers to viral load testing limit routine testing in many low and middle income countries (LMICs). Yet there is a great potential for increased viral load testing as costs decrease and as countries prioritize virological monitoring over clinical and or immunological criteria which have poor sensitivity and specificity for treatment failure.

Treatment guidelines from the World Health Organization (WHO) define virological failure based on HIV RNA levels greater than 5000 copies/mL in 2010 guidelines and 10,000 copies/mL in 2006 guidelines as these thresholds have been associated with higher rates of clinical progression and CD4 T-cell decline.^{1,2} In addition the WHO HIV drug resistance strategy for LMICs defines virological suppression based on a threshold of 1000 copies/mL.³ Guidelines in high income countries (HICs) define virological suppression based on thresholds of 50 copies/mL or below the limit of detection of the available assays.⁴⁻⁶

In addition to the variety of thresholds that can influence estimates of virological suppression, estimates can also be expressed as the proportion of those who initiated ART, the intention to treat (ITT) population; or the proportion who are still receiving ART, the on treatment (OT) population. The denominator of the ITT proportion also includes individuals commencing ART who subsequently die, or become lost to follow-up (LTFU) and therefore reflect patient or program level factors that influence mortality and LTFU.

ART program managers and their implementing partners require summary estimates of virological suppression for the purpose of establishing levels of ART clinic and program performance and setting targets. Furthermore they are necessary for researchers undertaking mathematical modeling of different strategies of ART delivery in LMICs. Recent reviews in this area focus on Sub-Saharan Africa and HIV drug resistance outcomes.^{7,8} There is a lack of summary estimates of virological suppression across LMICs based on alternative HIV RNA thresholds using OT and ITT analyses.

3. Objective

The objective of this systematic review was to establish summary estimates of virological suppression in LMICs after 12-months ART using different HIV RNA thresholds to define virological suppression in both OT and ITT analyses.

4. Methods

Criteria used to consider studies for inclusion:

- May include cross-sectional and cohort studies and may be prospective or retrospective
 - Clinical trials can be included
- Studies included if they are specifically designed to report virological outcomes or where it was a secondary finding
- Studies conducted in LMICs (Africa, Asia, Latin America)
 - Terms include “resource limited” or “resource constrained” or “developing countr*” or “low income countr*” or “low and middle income countr*”
 - Also include africa* or afrika* or "sub sahara*" or southern africa* or asia* or latin america* or south america*
- Participants receiving combination (≥ 3 agents) ART
 - “HIV” or “AIDS” or “human immunodeficiency virus” or “acquired immunodeficiency syndrome” AND “antiretroviral therapy” or “antiretroviral*” or “HAART” or “ART”
- Virological suppression outcomes
 - Combine the term “viral load” with “hiv rna”, “virologic*”, “resistance”, “genotype*” and “drug resistance”.
- 12 month outcomes
 - The term “time factors” combined with “1 year” or “12 month*”
- Conference abstract databases combined the terms “virologic” or “virological” with “suppression” or “failure”.
- Published in English
- Studies published after January 1, 2003
- Exclude studies of children (< 13 years old)
- Studies reporting on the proportion of individuals with a virological outcome after 12 months of ART.
 - The proportion below (or above) a threshold of HIV RNA in copies/mL from plasma after 12 months of ART
 - Study authors to be contacted if threshold of HIV RNA not reported
 - Exclude studies reporting change in HIV RNA
 - Duration of follow up has to be defined. If reports median duration only this has to be between 9 and 15 months
- See Appendix 1 for Medline search

Search methods for identification of studies

- Electronic searches.
 - Ovid MEDLINE (through PubMed)
 - Online conference abstract databases for the International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention; the International AIDS Conference and the Conference on Retroviruses and Opportunistic Infections (CROI) from 2009 to 2011
 - CROI

- Review titles of all oral and poster sessions and review all abstracts in sessions that based on session title (e.g. relevance to LMICs) could contain abstracts of interest (once abstract number found, then review with search function)
- IAS
 - Search abstracts in “program at a glance” using key terms as defined above (covers abstracts presented in oral sessions)
- Reference lists from recent reviews assessing virological outcomes in ART programs in LMICs to also searched

Data collection and analysis

- Selection of studies
 - Retrieved titles and abstracts will be assessed for full-text review using the criteria described above

Data extraction and management

- The following data will be abstracted to a Microsoft Excel spreadsheet:
 - Author, Journal, Year
 - Setting: countries, health facility level, type (public, private) and number
 - Number of study participants
 - Design
 - Characteristics of study population (age, gender, median baseline CD4)
 - ART regimens and proportion of population non-ART naïve
 - If available: proportion lost to follow-up (LTFU), died, proportion transferred care to another ART site, proportion stopped ART (either physician directed or patient initiated)
 - Study definition of virological suppression
 - Proportion meeting study definition of virological suppression
 - If there is only a study definition and a proportion of individuals with virological failure then convert into a proportion with virological suppression
 - Proportions were derived from a graph using either the exact value, or if they could be accurately estimated. If values were estimated from a graph this was noted.
 - Proportions with virological suppression for individuals OT and if the proportion died and LTFU is available then the proportion with virological suppression by ITT
- When more than one study reported on the same cohort of patients, include the publication containing the most detailed information

5. Statistical analysis and data synthesis

- Summary estimates of virological suppression will be determined and be considered in 2 ways
 1. Whether the proportions contributing to the summary estimate are OT or ITT
 2. By the threshold of HIV RNA used to determine virological suppression
 - Summary estimates could be grouped for different thresholds of HIV RNA e.g. higher thresholds 5,000-10,000 copies/mL, lower thresholds < 200 copies/mL and thresholds between 200 and 1,000 copies/mL)
 3. Report summary estimates as medians if the group of proportions are non-normally distributed or as weighted means if were normally distributed.

- Weighting of proportions will be by the inverse of its variance [$1 / (p \times (1-p) / n)$, where p is the proportion and n is the sample size].

References:

1. WHO. Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach. – 2006 rev: World Health Organization; 2006.
2. WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 rev.: World Health Organization; 2010.
3. Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. *Antivir Ther.* 2008; **13 Suppl 2**: 1-13.
4. Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA.* 2010; **304**(3): 321-33.
5. DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents 2012 [cited May 12 2012]; Available from: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>
6. Asboe D, Aitken C, Boffito M, Booth C, Cane P, Fakoya A, et al. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med.* 2012; **13**(1): 1-44.
7. Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. *Lancet Infect Dis.* 2010; **10**(3): 155-66.
8. Gupta RK, Hill A, Sawyer AW, Cozzi-Lepri A, von Wyl V, Yerly S, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. *Lancet Infect Dis.* 2009; **9**(7): 409-17.

APPENDIX 1 - Search Strategy

- 1 exp Antiretroviral Therapy, Highly Active/ (13213)
- 2 exp HIV Infections/ (198617)
- 3 exp HIV/ (70704)
- 4 exp Anti-Retroviral Agents/ (51271)
- 5 1 or 2 or 3 or 4 (237850)
- 6 (resource limited or resource constrained or developing countr* or low income countr* or "low and middle income countr*").tw. (32450)
- 7 (africa* or afrika* or "sub sahara*" or southern africa* or asia* or latin america* or south america*).tw. (166542)
- 8 exp Africa/ (151724)
- 9 exp Asia/ (394665)
- 10 caribbean region/ or central america/ or latin america/ or south america/ (15057)
- 11 6 or 7 or 8 or 9 or 10 (657853)
- 12 exp African Americans/ (33865)
- 13 exp Asian Americans/ (4265)
- 14 12 or 13 (37133)
- 15 11 not 14 (638182)
- 16 exp Viral Load/ (15677)
- 17 hiv rna.tw. (3224)
- 18 virologic*.tw. (14502)
- 19 (resistance or genotyp* or drug resistance).tw. (478442)
- 20 16 or 17 or 18 or 19 (501445)
- 21 5 and 15 and 20 (3361)
- 22 (1 year or one year or 12 month* or twelve month* or first year*).tw. (253768)
- 23 exp Time Factors/ (884377)
- 24 22 or 23 (1107096)
- 25 21 and 24 (411)
- 26 limit 25 to (english language and yr="2003 -Current") (338)
- 27 limit 26 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)") (90)
- 28 26 not 27 (248)