

Title: Strategies for optimizing HIV monitoring among adults, children and pregnant women living with HIV receiving antiretroviral therapy: a systematic review

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1. PICO question

Population	People living with HIV taking antiretroviral therapy (including adults, children and pregnant women)
Interventions	Routine monitoring with CD4 count versus viral load
Reference standard or comparators	Routine management with clinical decision-making (present in both arms of the study)
Outcomes	Mortality (primary), morbidity, especially AIDS-associated illness (secondary), adverse outcomes
Study design	Evaluation studies, conference abstracts and ongoing studies included
Other	No language, date or geographical restrictions; no restrictions on duration of ART

Population	People living with HIV taking antiretroviral therapy (including adults, children and pregnant women)
Interventions	Routine viral load monitoring
Reference standard or comparators	Viral load thresholds for switching ART – 5000, 2000 and 1000 and less copies/ml (thresholds for children: (1) 5000 copies/ml; (2) 10 000 copies/ml; and (3) 30 000 copies/ml)
Outcomes	Mortality, morbidity, virological suppression, resistance, switching rates, adverse outcomes
Study design	Evaluation studies, conference abstracts and ongoing studies included
Other	No language, date geographical restrictions; no restrictions on duration of ART; studies with adults, children and pregnant women included

2. Search strategy

ART term

1 exp Antiretroviral Therapy, Highly Active/

2 exp Anti-Retroviral Agents/

3 Antiviral Agents/

4 (anti adj3 hiv) OR antiretroviral OR (anti adj3 retroviral) OR HAART OR (anti adj3 acquired immunodeficiency) OR (anti adj3 acquired immunodeficiency) OR (anti adj3 acquired immunodeficiency)

OR (anti adj3 acquired immune-deficiency) OR (anti adj3 (acquired immun* adj3 deficiency))

5 1 or 2 or 3 or 4

Monitoring term

6 CD4 lymphocyte count/

7 viral load/

8 RNA, Viral/

9 Monitoring, Physiologic/

10 Monitoring, immunologic/

11 Treatment failure/

12 (viral adj2 load) OR (drug adj2 monitoring) OR (treatment adj2 outcome) OR (CD4 adj3 T-cell) OR (CD4 adj3 cell adj3 count)

13 5 and (6 or 7 or 8 or 9 or 10 or 11 or 12)

HIV term

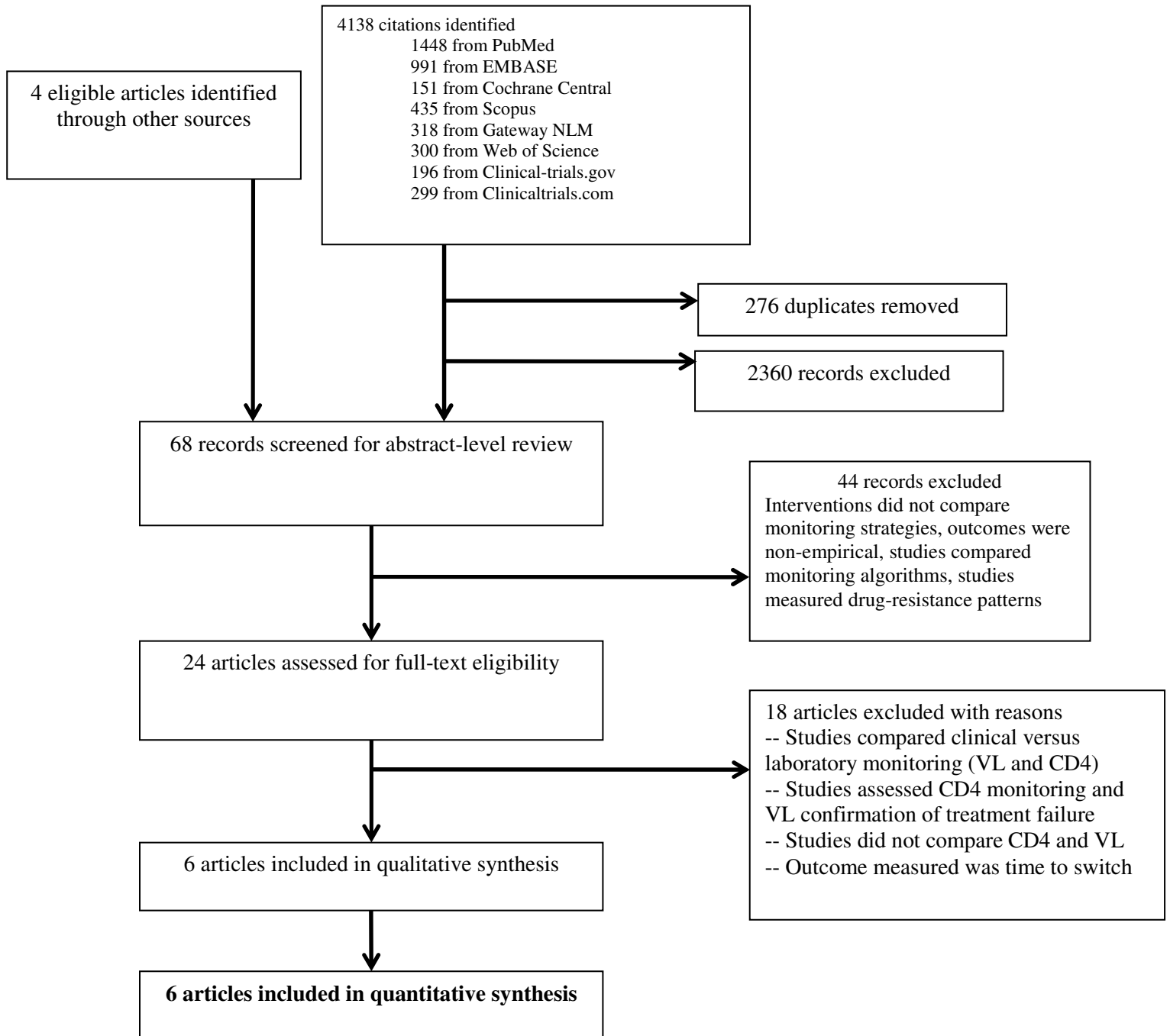
14 HIV Infections/

15 HIV/

16 hiv OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immunodeficiency virus OR human immuno-deficiency virus OR human immunodeficiency virus OR (human immun* adj3 deficiency virus) OR acquired immunodeficiency syndrome OR acquired immunodeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immunodeficiency syndrome OR (acquired immun* adj3 deficiency syndrome)

17 13 and (14 or 15 or 16)

3. Flow diagram of screening process



4. Evidence summaries

Background

Monitoring people living with HIV is critical for determining when to switch from first-line to second-line ART and what factors underpin clinical, immunological or virological failure. Advances in point-of-care technology expand the potential use of viral load technology for monitoring in several settings, but evidence is needed to clarify their appropriate use. The purpose of this study is to systematically review original research on CD4 and viral load monitoring of people living with HIV and compare various viral load thresholds for switching to second-line ARV regimens. This was prepared in November 2012 at the request of WHO to inform the development of HIV guidelines.

Objective

To investigate CD4 monitoring and viral load monitoring of adults, children, and pregnant women living with HIV in low-income, middle-income and high-income settings and examine optimal viral load thresholds for switching to second-line ARV regimens. A secondary objective was to examine cost-effectiveness analyses to inform modelling.

Search strategy

We formulated a comprehensive search strategy in an attempt to identify all relevant studies regardless of language or publication status. In November 2012 we searched the following electronic journal and trial databases: MEDLINE, EMBASE, CENTRAL, Scopus, NLM Gateway (for HIV/AIDS conference abstracts before 2005), Conference on Retroviruses and Opportunistic Infections, International AIDS Conference and International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention from 2005 to 2009, Web of Science Conference Proceedings since 1990, Clinicaltrials.gov and Current Controlled Trials. We contacted researchers and relevant organizations and checked reference lists for all included studies.

Selection criteria

We selected studies that examined routine clinical monitoring, immunological monitoring (CD4 measurement) or virological monitoring (viral load measurement) or examined viral load thresholds to inform switching to second-line regimens. Study types included randomized controlled trials and observational studies.

Data collection and analysis

One author performed initial screening. Two authors performed detailed screening. Two authors independently assessed study eligibility, extracted data and graded methodological quality. A third reviewer resolved differences.

Main findings

A total of nine studies were identified, including seven randomized controlled trials (RCTs) and two observational studies. All seven RCTs (Mermin et al. 2011, Jourdain et al. 2011, Koethe et al. 2011, Babiker et al. 2011, Mugenyi et al. 2010, Laurent et al. 2011, Saag et al. 2012) were complete, with two available in manuscript form except two studies that were only available as abstracts (Jourdain et al. 2011, Saag et al. 2012). Of the evidence available, the following five designs were identified: clinical versus clinical + immunological; clinical versus clinical + virological; clinical + immunological versus clinical + immunological + virological; clinical + immunological versus clinical + virological; and comparisons of one viral load threshold to another viral threshold.

- 1) **Clinical versus clinical + immunological.** Two RCTs (Mermin et al. 2011, Mugenyi et al. 2010) found increased AIDS-defining illness and mortality in routine clinical monitoring compared to immunological monitoring (moderate- to high-quality evidence).

- 2) **Clinical versus clinical + immunological + virological.** One RCT (Laurent et al. 2011) found no difference between mortality and disease progression between these two groups but found a greater increase in mean CD4 cell count at 24 months in the clinical + immunological + virological study arm (moderate-quality evidence).
- 3) **Clinical + immunological versus clinical + immunological + virological.** Two RCTs (Mermin et al. 2011, Saag et al. 2012) and one observational study (Keiser et al. 2011) among adults found no difference in clinical and immunological monitoring compared to clinical and immunological and virological monitoring in terms of mortality (moderate-quality evidence) and new AIDS-defining illness (moderate-quality evidence).
- 4) **Clinical + immunological versus clinical + virological.** An RCT (Jourdain et al. 2011) among adults found no difference in clinical failure (low-quality evidence), switch to second-line regimens (low-quality evidence) and resistance mutations (low-quality evidence).
- 5) **Viral load threshold comparisons.** One RCT (Babiker et al. 2011) among children found no difference in virological suppression or resistance mutations between children switched at a viral threshold of 1000 copies/ml compared to 30 000 copies/ml (medium). Based on one observational study among children (Siberry et al. 2012), viral load thresholds of 2600 and 30 000 copies/ml predicted WHO Stage 3 or 4 events (low-quality evidence).

Authors' conclusions

- Moderate-quality evidence supports the use of CD4 monitoring compared to routine clinical monitoring among people living with HIV receiving ART.
- Evidence is limited on the additional benefit of viral load monitoring and viral load thresholds among people living with HIV receiving ART.
- No studies on pregnant women were identified, no studies on viral load thresholds among adults and no studies among children comparing viral load and CD4 count monitoring.
- Point-of-care CD4 monitoring feasibility and accuracy are excellent, but point-of-care viral load measurement lags behind CD4 monitoring in feasibility and accuracy.
- Moderate-quality evidence from two randomized controlled trials (Mermin et al. 2011, Mugenyi et al. 2010) among adults suggests that clinical and immunological monitoring offers mortality and morbidity benefits compared to clinical monitoring alone.
- Moderate-quality evidence from two randomized controlled trials among adults (Mermin et al. 2011, Saag et al. 2012) suggests that there is no difference between clinical + immunological + virological monitoring and clinical + immunological monitoring. Complete data from the one other randomized controlled trial (Jourdain et al. 2011) will help inform the development of appropriate HIV monitoring guidelines.
- Two small studies (Babiker et al. 2011, Siberry et al. 2012) provided low- to medium-quality evidence on which viral load threshold should be used to guide switching to second-line regimens. One randomized controlled trial (Babiker et al. 2011) found no difference in virological suppression or resistance mutations among children switched at a viral threshold of 1000 copies/ml compared to 30 000 copies/ml.
- Further research is needed to create a stronger evidence base for developing HIV monitoring guidelines.

5. Quality assessment

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Mermin 2011	+	?	–	+	+	?
Jourdain 2011	?	?	?	?	?	?
Keiser 2011	–	–	–	–	–	–
Koethe 2011	+	–	–	?	?	?
Siberry 2012	–	–	–	?	?	?
Babiker 2011	+	+	–	+	+	+
Riddler 2007	?	?	–	?	–	?
Kityo (unpublished)	?	?	–	–	+	?
Laurent 2011	+	+	–	+	+	+
Saag 2011	?	?	?	?	?	?
DART 2010	+	+	–	+	+	+

Key: "+" denotes present in study, "–" denotes absent in study, and "?" denotes unable to assess

6. Bibliography of included studies

1. Babiker A, Castro nee Green H, Compagnucci A, Fiscus S, Giaquinto C, Gibb DM, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. *Lancet Infectious Diseases* 2011; 11(4): 273-83.
2. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, Traisaithit S, Barbier S, Techapornroong S, et al. PHPT-3: a randomized clinical trial comparing CD4 vs viral load ART monitoring/switching strategies in Thailand. 18th Conference on Retroviruses and Opportunistic Infections; 2011; Boston, MA.
3. Keiser O, Chi BH, Gsponer T, Boulle A, Orrell C, Phiri S, et al. Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in southern Africa. *AIDS* 2011; 25(14): 1761-9.
4. Kityo C, Gibb DM, Gilks CF, Goodall RL, Mambule I, Pontiano K, et al. High rate of viral suppression and low switch rate to second-line antiretroviral therapy among HIV-infected patients followed over five years without virological monitoring. Unpublished manuscript. 2012.
5. Koethe JR, Westfall AO, Luhanga DK, Clark GM, Goldman JD, Mulenga PL, et al. A cluster randomized trial of routine HIV-1 viral load monitoring in Zambia: study design, implementation, and baseline cohort characteristics. *PLoS ONE* 2010; 5(3).

6. Laurent C, Kouanfack C, Laborde-Balen G, Aghokeng AF, Mbougua JB, Boyer S, et al. Monitoring of HIV viral loads, CD4 cell counts, and clinical assessments versus clinical monitoring alone for antiretroviral therapy in rural district hospitals in Cameroon (Stratall ANRS 12110/ESTHER): a randomised non-inferiority trial. *Lancet Infectious Diseases* 2011; 11(11): 825-33.
7. Mermin J, Ekwaru JP, Were W, Degerman R, Bunnell R, Kaharuzza F, et al. Utility of routine viral load, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial. *BMJ* 2011; 343: d6792.
8. Mugenyi P, Walker AS, Hakim J, Munderi P, Gibb DM, Kityo C, et al. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet* 2010; 375(9709): 123-31.
9. Saag MS, Westfall A, Luhanga DK, Mulenga PL, Chi BH, Mulenga L, et al. A cluster randomized trial of routine vs discretionary viral load monitoring among adults starting ART: Zambia. 19th Conference on Retroviruses and Opportunistic Infections. Seattle, WA; 2012.
10. Siberry GK, Harris DR, Oliveira RH, Krauss MR, Hofer CB, Tiraboschi AA, et al. Evaluation of viral load thresholds for predicting new World Health Organization stage 3 and 4 events in HIV-infected children receiving highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes* 2012; 60(2): 214-8.