Optimal strategies for monitoring response to antiretroviral therapy in HIV-infected adults, adolescents, children and pregnant women: a systematic review

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Objective: The objective of this review was to examine different monitoring strategies (clinical, immunologic (CD4\textsuperscript{+} T cell count measurement) and virologic (viral load measurement)) to inform revision of the 2013 WHO guidelines for antiretroviral therapy (ART) in low and middle-income countries.

Design: A systematic review.

Methods: We searched 10 databases, reference lists of included research studies and contacted experts in an attempt to identify all relevant studies regardless of language or publication status. We included both randomized controlled trials (RCTs) and observational studies. We selected studies that examined routine clinical monitoring (CM), immunologic monitoring (IM) or virologic monitoring (VM). CM involved clinical evaluation and basic laboratory blood testing without CD4\textsuperscript{+} T cell count or viral load. Two authors independently assessed study eligibility, extracted data and graded methodological quality.

Results: A total of six studies were identified, including five RCTs and one observational study. Two RCTs among adults found an increased risk of AIDS-defining illness and mortality in CM compared to CM + IM. Two studies compared CM + IM to CM + IM + VM, with one finding a mortality advantage in the CM + IM + VM group. Duration of viremia and time to switching to a second-line regimen were longer in CM + IM compared to CM + IM + VM. Only one trial was conducted in children, and showed no difference in mortality comparing CM and CM + IM. No studies specifically studied pregnant women.

Conclusion: CM + IM was shown to be beneficial in terms of a combined mortality and morbidity endpoint compared to CM alone. VM was associated with shorter duration of viremia and higher rates of switching, but an impact on mortality was not consistently shown. Pooled outcome estimates were possible with comparison of only CM to CM + IM. Further HIV research on different VL monitoring strategies is required. These data support the recommendation in the 2013 WHO ART guidelines for the use of VM to confirm and diagnose ART failure, and for the use of IM + CM when VM is not available.

Keywords: antiretroviral therapy, HIV, immunologic, monitoring, systematic review, virologic, WHO

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Introduction

In the past two years, there has been a 60% increase in the number of individuals taking antiretroviral therapy (ART) and there are now 9.7 million individuals on ART worldwide [1]. Over two-thirds of these individuals are in low and middle-income countries. This has been achieved through scaling up systems for delivering HIV ART at the population level based on a public health approach of simplified and standardized treatment and monitoring in accordance with WHO guidelines [2,3]. Yet, this progress has also prompted the need to re-evaluate optimal strategies for routine monitoring of ART response and detection of treatment failure. Most HIV monitoring guidelines in low-income settings define treatment failure and ART switching criteria according to clinical monitoring with or without immunologic monitoring (CD4+ T cell count measurement), consistent with the 2006 [4,5] and 2010 [6,7] WHO guidelines. In contrast, routine virologic monitoring (viral load measurement every 3–6 months) has been the standard of care for detection of treatment failure and the basis for switching ART regimens in many middle and high-income nations for over a decade [8].

There are concerns with the use of clinical and immunologic monitoring alone. Multiple studies, including a systematic review undertaken to inform the development of the 2013 WHO guidelines have highlighted the poor positive predictive value of the 2010 WHO clinical and immunologic criteria to identify virologic failure [9,10]. This contributes to delayed switching to second-line regimens as well as misdiagnosis of treatment failure leading to unnecessary switching. Virologic monitoring also offers the potential to assess early ART response, thereby providing an opportunity to improve adherence [11]. Furthermore, technological developments in point-of-care immunologic and virologic monitoring allow decentralized monitoring in many locations where monitoring was not feasible in the past [12].

In 2012, the WHO started the process of updating guidelines on the use of ART for treatment and prevention of HIV infection in adults, pregnant women, adolescents and children [13]. This systematic review was undertaken to better understand optimal monitoring strategies for HIV-infected individuals. Our review focused on evaluating the medical and public health benefit of different HIV monitoring strategies without considering cost or availability of monitoring tools. We examined studies that compared different strategies for routine monitoring of ART response, including clinical monitoring (CM), immunologic monitoring (IM), and virologic monitoring (VM) among all available populations, including HIV-infected adults, pregnant women, adolescents and children. The objective of this review is to update evidence on ART monitoring strategies to inform revision of the 2013 WHO guidelines for ART in low and middle-income countries.

Materials and methods

We examined studies that compared CM, IM and VM (or combinations of these strategies) among adults, adolescents, children and pregnant women (Appendix 1, http://links.lww.com/QAD/A500). CM was defined as clinical evaluation (medical history and physical examination by a trained healthcare professional) that may include basic laboratory testing, but not CD4+ T cell count or viral load measurements, usually at 3–6 month intervals. IM was defined as measurement of absolute CD4+ T cell count values for adults or CD4+ T cell count percentage measurement for children, usually every 6 months. VM referred to routine measurement of plasma viral load at 6–12 month intervals, but not the use of confirmatory viral loads in those with evidence of clinical and/or immunologic failure. Outcomes examined included morbidity and mortality, drug resistance, switch rates to second-line ART and adherence. We did not examine strategies for monitoring ART drug toxicities because these are largely ART-specific and have been described elsewhere [14–16]. Studies that examined only different frequencies of monitoring or thresholds for switching to second-line ART, optimal frequency of monitoring or cost-effectiveness were excluded. The review was reported following PRISMA and AMSTAR guidelines and registered in PROSPERO (CRD42013004358).

Search strategy and identification of studies

No date, age, geographic or language restrictions were used in this search, and we included all citations identified through 20 April 2013. We searched the following electronic journal and trial databases: Pubmed, EMBASE, Cochrane Central, Sciverse 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 2012, Web of Science Conference Proceedings since 1990, ClinicalTrials.gov, PsycINFO and Current Controlled Trials. We contacted researchers and relevant organizations and screened reference lists of all included studies to identify additional eligible studies. Search terms are included in Appendix 1, http://links.lww.com/QAD/A500.

Study selection and data abstraction

Two reviewers (J.T. and C.B.) independently screened all citations and undertook independent data abstraction using a standardized form (Fig. 1). Discrepancies between abstracted data accounted for less than 3% of the total data.
and were resolved by a third independent individual. Authors of all five RCTs were contacted for more information about items not reported in the manuscript and three replied. Full research articles, brief reports, abstracts and descriptions of clinical trials evaluating HIV monitoring were included. We selected studies that compared combined monitoring strategies of CM, IM or VM (Appendix 2, http://links.lww.com/QAD/A500).

Quality assessment
Two forms of quality assessment were undertaken to identify the strengths and weaknesses of the research studies. First, in accordance with the WHO Guidelines Review Committee guidance and the Cochrane group, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to summarize the quality of the evidence \[17,18\]. GRADE classifies the quality of evidence into four categories – high quality, moderate quality, low quality and very low quality – on the basis of the consideration of study attributes. Evidence from RCTs starts as high but can be downgraded based on study limitations, including inconsistency of results, indirectness of evidence, imprecision, risk of bias including publication bias. Evidence from observational studies starts at low but can be upgraded if the effect size is very large, or if all possible confounders would decrease the magnitude of effect of the intervention [18]. Second, recognizing the limitations of the GRADE approach, we also examined the quality of RCTs and observational studies according to more extensive checklists that have been designed to evaluate quality of reporting from these types of studies. The CONSORT checklist [19] evaluated RCT manuscripts based on 25 items. The STROBE checklist [20] evaluated observational studies based on 22 items within similar categories. Potential conflicts of interest were also examined based on reported funding sources.

Data analysis
For each comparison of monitoring strategies, we reported estimated relative risks (RR) and the 95% confidence interval (CI) for all key outcomes for each of the published studies. We also examined the appropriateness of pooling research findings. Two studies compared the same monitoring strategies and reported comparable mortality outcomes, and these outcomes were therefore pooled using a fixed effects model to generate a summary effect size [21], in addition to

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Fig. 1. Flow chart of study selection process.
reporting the outcomes separately for each study. Other study results were not pooled because of differences in monitoring strategies compared or outcomes, or insufficient data. Publication bias was not formally assessed because there were fewer than 10 included studies.

Results

Our search strategy identified 4138 citations (Fig. 1). After removing duplicates and titles not relevant to ART response monitoring, a total of 68 abstracts were further screened. Twenty-four full-text published studies were screened and 18 studies were excluded [9,22–38]. Six studies were included in the final review [39–44].

Description of included studies

Table 1 summarizes the characteristics of the included studies. Five studies were RCTs [39,41–44] and one study was an observational study [40]. Five studies were undertaken in Africa [40–44] and one in Asia (Table 1) [39]. Three studies were undertaken in multiple countries [40,43,44] and three in a single country [39,41,42]. The observational study included 99,643 individuals [40] and the five RCTs ranged in size from 459 [41] to 3321 participants [44]. Five studies included only adults [39–42,44] and one examined children and adolescents [43]. Three studies specifically excluded pregnant women [41,43,44] (Table 3). The median CD4+ T cell count prior to initiation of monitoring was less than 300 cells/µl in all studies. Median follow-up time ranged from 2 to 4.9 years. Two studies only included ART-naive individuals [40,41] (Table 1). Studies compared the following treatment response monitoring strategies: CM; CM + IM; CM + VM; CM + IM + VM. All studies examined mortality and four studies included WHO stage 3 and 4 events [41–44].

Comparison of clinical monitoring and clinical monitoring together with immunologic monitoring and virologic monitoring

Three RCTs compared CM with CM + IM (Table 2) [42–44]. Both RCTs in adults found a significant advantage of CM + IM compared to CM when examining a combined morbidity and mortality endpoint (6.0 events per 100 person-years in the CM + IM group compared with 7.6 events per 100 person-years in the CM group in one RCT; [42]; 5.2 events per 100 person-years in the CM + IM group compared with 6.9 events per 100 person-years in the CM group in another RCT [44]). Among the adult RCTs, both found a mortality benefit in the CM + IM group. One study found significantly increased mortality in the CM group (hazard ratio 1.52, 95% CI 1.10–1.65, P < 0.001) [44] and one found a nonsignificant trend in the same direction (hazard ratio 1.43, 95% CI 0.92–2.21, P = 0.10) (Table 3) [42]. Pooling the mortality outcome for these two studies comparing CM and CM + IM groups showed increased mortality in the CM group with a pooled hazard ratio estimate of 1.36 (95% CI 1.14–1.64). One adult RCT examining switch rates to a second-line regimen found a higher switch rate to second-line ART of 22% in the CM + IM group at 5 years than 19% in the CM group (P = 0.03) [44].

The only RCT among children showed no difference between CM compared to CM + IM in terms of a combined endpoint of WHO stage four events or mortality (hazard ratio 1.13, 95% CI 0.73–1.73, P = 0.59) [43]. However, in year one, WHO stage four events or mortality were lower in the CM group (P = 0.20). During years 2–5, WHO stage 4 events or mortality were higher in the CM group (P = 0.002).

Comparison of clinical monitoring along with immunologic monitoring and clinical monitoring along with virologic monitoring

One RCT compared CM + IM + VM to CM [41] (Table 2). This study found no difference between CM and CM + IM + VM in terms of combined mortality/morbidity endpoint (26.6 events per 100 person-years in the CM group compared with 19.9 events per 100 person-years in the CM + IM + VM group; P = 0.25) or mortality alone (11.5 deaths per 100 person-years in the CM group compared with 8.8 deaths per 100 person-years in the CM + IM + VM group; P = 0.11) [41]. The hazard ratio comparing CM to CM + IM + VM was 1.31 (95% CI 0.83–2.06). The CM + IM + VM arm had significantly higher switch rates to second-line ART (6 compared with 0%, but the frequency of drug resistance mutations was similar at 10% [41].

Comparison of clinical monitoring along with immunologic monitoring and clinical monitoring along with virologic monitoring

Two studies compared CM + IM to CM + IM + VM [40,42], including one RCT [42] and one observational study [40] (Table 2). The RCT showed no difference between the two groups in terms of mortality, although the observational study [40] found a 3-year mortality rate of 6.3% (95% CI 6.0–6.5) in the CM + IM group and 4.3% (95% CI 3.9–4.8) in the CM + IM + VM group (P < 0.001). Switch rates to second-line ART regimens at the end of year 3 were also higher in the CM + IM + VM group at 9.8% (95% CI 9.1–10.5) [40] compared with 2.1% (95% CI 2.0–2.3) in the CM + IM group. None of these studies directly measured differences in adherence or onward HIV transmission.

Comparison of clinical monitoring along with immunologic monitoring and clinical monitoring along with virologic monitoring

One adult RCT compared CM + IM with CM + VM [39], but this study was only available in abstract form (Table 2). This study found no difference in either
<table>
<thead>
<tr>
<th>First author</th>
<th>Sample size</th>
<th>Location</th>
<th>Population</th>
<th>Median CD4+ T cell count (cells/µl in adults)(^b)</th>
<th>Median age in years (IQR)</th>
<th>Study design</th>
<th>Control arm(s)</th>
<th>Intervention arm(s)</th>
<th>Follow-up (median, years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jourdain et al.(^a) [39]</td>
<td>716</td>
<td>Thailand</td>
<td>Adults, 62% women, CD4+ T cell count 50–250 cells/µl, not hepatitis B or C coinfectected</td>
<td>144</td>
<td>36 (31–41)</td>
<td>RCT</td>
<td>CM + IM</td>
<td>CM + VM</td>
<td>NR</td>
</tr>
<tr>
<td>Keiser et al. [40]</td>
<td>99,643</td>
<td>South Africa, Malawi, Zambia</td>
<td>Adults, 65% women, ART-naïve patients aged 16 years and older who started ART with an NNRTI-based regimen and who had at least 1 day of follow-up</td>
<td>132, 93</td>
<td>34 (30–41)</td>
<td>Observational</td>
<td>CM + IM</td>
<td>CM + IM + VM</td>
<td>3</td>
</tr>
<tr>
<td>DART [44]</td>
<td>3,321</td>
<td>Uganda and Zimbabwe</td>
<td>Adults with CD4+ T cell count &lt;200 cells/µl, 64% women, able to and likely to attend follow-up, likelihood of good compliance, no acute infection or tuberculosis therapy ongoing, no chemotherapy for malignancy, not pregnant or breastfeeding, laboratory values allowed initiation of ART</td>
<td>86</td>
<td>36 (18–73)</td>
<td>RCT</td>
<td>CM</td>
<td>CM + IM</td>
<td>4.9</td>
</tr>
<tr>
<td>Laurent et al. [41]</td>
<td>459</td>
<td>Cameroon</td>
<td>Adults, 70% women, 18 years old or older with confirmed HIV-1 group M infection, WHO clinical stage 3 or 4 or 2 with total lymphocyte count of less than 1200 cells/µl, likely to attend follow-up appointments, without active tuberculosis or malignancy or psychiatric disorders or hepatocellular insufficiency or previous ART or use of steroids or other experimental drugs, not pregnant</td>
<td>179, 182</td>
<td>36 (30–44)</td>
<td>RCT</td>
<td>CM</td>
<td>CM + IM + VM</td>
<td>2</td>
</tr>
<tr>
<td>Mermin et al. [42]</td>
<td>1,094</td>
<td>Uganda</td>
<td>Adults with CD4+ T cell count &lt;250 cells/µl or WHO stage 3 or 4 disease, 67% women, 18 years and older, clients with CD4+ T cell count less than 250 cells/µl or severe HIV disease, AST less than five times the upper limit of normal, creatinine clearance greater than 0.42 ml/s, Karnofsky score greater than 40%, no prior use of nevirapine for PMTCT</td>
<td>129</td>
<td>39 (32–44)</td>
<td>RCT</td>
<td>CM</td>
<td>CM + IM or CM + IM + VM</td>
<td>3</td>
</tr>
<tr>
<td>ARROW [43]</td>
<td>1,206</td>
<td>Uganda and Zimbabwe</td>
<td>Aged 3 months to 17 years eligible for ART, 51% female, age 3 months to 17 years old who met WHO 2006 criteria for ART initiation, without acute infection or taking contraindicated drugs or adherence issues or laboratory abnormalities that contraindicate ART or pregnant or breastfeeding</td>
<td>12.5%, 12.0%</td>
<td>5.9 (2.2–9.2)</td>
<td>RCT</td>
<td>CM</td>
<td>CM + IM</td>
<td>4.0</td>
</tr>
</tbody>
</table>

CM, clinical monitoring; FU, follow-up time; IM, immunologic monitoring; NR, not reported; VM, virologic monitoring.

\(^a\)Only abstract available.

\(^b\)Three studies reported overall median CD4+ T cell count and three studies reported median CD4+ T cell count by study arm. All CD4+ T cell counts were at baseline prior to assignment except for Keiser et al. [40].
mortality (3.4% CM + IM vs. 4.3% CM + VM, \( P = 0.57 \))

or a composite endpoint of mortality, new AIDS-defining event, or CD4\(^+\) T cell count of 50 cells/\( \mu l \) or less at 3 years (7.4% CM + IM vs. 8.0% CM + VM). There was a trend towards higher switch rates in the CM + IM group (7.2% vs. 5.1%, \( P = 0.10 \)). The median duration of viremia of more than 400 copies/ml was twice as long at 15.8 months in the CM + IM group compared with 7.2 months in the CM + VM group (\( P = 0.002 \)).

### Quality assessment

All four RCTs with full texts available \([41–44]\) were rated as of good quality on the basis of the CONSORT criteria, fulfilling 94–97% of 34 key indicators (Appendix 3, http://links.lww.com/QAD/A500). Minor limitations were that three out of four studies did not explicitly state why the study was stopped and none of the articles had publicly available links to the full trial protocol. The RCT abstract \([39]\) achieved 12/17 (71%) of CONSORT abstract indicators (Appendix 4, http://links.lww.com/QAD/A500) and the observational study \([40]\) achieved 24/30 (80%) of STROBE indicators (Appendix 5, http://links.lww.com/QAD/A500). On the basis of GRADE quality of evidence assessment, the observational study \([40]\) was ranked as low and each of the RCT studies \([39,41–44]\) as moderate (Appendices 6–8, http://links.lww.com/QAD/A500). All of the studies described the research funders and none of the research studies noted support from manufacturers of CD4\(^+\) T cell count or viral load measurement technology.

### Discussion

Understanding optimal strategies for HIV monitoring is critical as health systems expand routine delivery of ART worldwide. Our review extends a previous Cochrane systematic review \([45]\), which only examined data from two RCTs in abstract form. Our review benefited from each of these two RCTs being available as published manuscripts \([42,44]\) alongside recently available data from four other studies. Our review found that ART monitoring strategies that included CM along with IM had better outcomes than strategies that only provided CM, drawing on RCT data from both adults and children. The addition of routine VM resulted in some additional benefit. Although limitations in the data precluded a formal meta-analysis, this review provides an evidence base informing recommendations about routine monitoring of HIV-infected individuals on ART.
Table 3. Adult mortality and switch rate comparison for antiretroviral therapy response arranged by Comparison Group.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study</th>
<th>Mortality (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mortality Hazard Ratio and 95% CI&lt;sup&gt;b&lt;/sup&gt;</th>
<th>New WHO stage 3–4 events or death&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Morbidity or mortality hazard Ratio and 95% CI</th>
<th>Switch rates to second-line ART</th>
<th>Switch rate hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM vs. CM + IM</td>
<td>DART [44]</td>
<td>2.9 (95% CI 2.6–3.4) CM; 2.2 (95% CI 1.9–2.5) 4.9 CM at 3 years; 4.0 CM + IM</td>
<td>1.35 (1.10–1.65) CM; 1.31 (1.14–1.51)</td>
<td>6.9 (95% CI 6.3–7.6) CM; 5.2 (95% CI 4.7–5.8) 7.6 CM; 6.0 CM + IM</td>
<td>19% at 5 years CM; 22% at 5 years CM + IM</td>
<td>1.06 (0.91–1.23)</td>
<td></td>
</tr>
<tr>
<td>Mermin et al. [42] Pooled</td>
<td>CM + IM</td>
<td>1.43 (0.92–2.21) 4.0 CM + IM</td>
<td>1.10 (0.69–1.75) 6.0 CM + IM 4.8 CM + IM + VM</td>
<td>1.23 (0.82–1.84) 15% at 3 years CM; 44% at 3 years CM + IM</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Keiser et al. [42]</td>
<td>CM + IM + VM</td>
<td>6.3% (95% CI 6.0–6.5) 4.0 CM + IM; 3.7 CM + IM + VM</td>
<td>1.72 (1.52–2.00) NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Laurent et al. [41]</td>
<td>CM + IM + VM</td>
<td>11.5 CM; 8.8 CM + IM + VM</td>
<td>1.31 (0.83–2.06) 26.6 CM; 19.9 CM + IM + VM</td>
<td>1.30 (0.94–1.80) 0% CM; 6% CM + IM + VM</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Mermin et al. [42]</td>
<td>CM + IM + VM</td>
<td>4.9 CM; 3.7 CM + IM + VM</td>
<td>1.57 (1.00–2.46) 7.6 CM; 4.8 CM + IM + VM</td>
<td>1.83 (1.25–2.69) 11% at 3 years CM; 44% at 3 years CM + IM</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

CM, clinical monitoring; IM, immunologic monitoring; NR, not reported; VM, virologic monitoring.

<sup>a</sup>DART, Laurent et al. [41], Mermin et al. [42] and ARROW reported mortality as deaths per 100 person-years; Keiser et al. [40] reported mortality as percentage died.

<sup>b</sup>Reference group in each of these comparisons is the group with less monitoring.
scaling up ART monitoring worldwide. Expanding
ART monitoring access, ensuring quality control systems
and strengthening health systems are all linked to the
overall success or failure of HIV monitoring programmes.
First, availability of CM and VM in low and middle-
cIncome countries is uneven [49], despite evidence that
decentralized community-based HIV testing is associated
with better access and outcomes [50]. Expanding HIV
monitoring services at clinical and nonclinical settings
may increase the total number of HIV-infected indi-
viduals who receive appropriate ART monitoring [51].
Novel financing mechanisms such as UNITAID along-
side advances in point-of-care technology can accelerate
this process [12]. Second, comprehensive quality control
systems are also necessary for the implementation of HIV
monitoring technologies [52]. Several quality assessment
projects have been undertaken [53–55], but none have
been implemented on a large scale. Ensuring quality
control will be especially important as HIV monitoring
becomes decentralized and implemented at lower level
healthcare facilities with limited capacity. Finally,
monitoring technology alone does not guarantee
appropriate clinical action resulting from diagnosis of
virologic failure [49]. Local staff training and responsive
health systems are necessary to reap the benefits of
enhanced monitoring [56,57].

Our study has several limitations. First, most of the studies
had follow-up of less than 3 years, and longer follow up
will be necessary to examine the impact on mortality
and development of drug resistance. Second, a pooled
estimate of mortality was only done for one comparison
of CM compared with CM + IM. For all the other
monitoring strategy comparison studies, there were substantive differences between studies that precluded
pooling of outcome measures. One key trial [39] was only
available in abstract form during our data analysis.
In addition, HIV drug resistance data were only reported
in one published manuscript [41], although this is
important to understand the limitations of routine moni-
toring without viral load measurement. Third, cost-
effectiveness considerations are important with respect to
implementation and scale up in low and middle-income
countries, but were not the focus of this review. However,
cost-effectiveness analyses of routine HIV treatment
monitoring strategies have not been conclusive [58,59].
Fourth, most of the studies were conducted in HIV-
infected adults. There were no studies specifically among
pregnant women, and only one RCT among children.
Finally, although we assessed each study for bias, we
were not able to formally evaluate for publication bias
because of the limited number of studies. But given
the complexity and cost of organizing HIV monitoring
research studies, we doubt that unpublished studies exist
that would compromise the review conclusions.

Our review highlights a number of HIV monitoring
research priorities moving forward. In light of the WHO
recommendations for earlier initiation of ART, the
need for scale-up of viral load monitoring relative to
CD4+ T cell count monitoring is likely to increase,
which needs to be informed by timely implementa-
tion research. Evaluation of monitoring strategies in the
context of ART initiation at higher CD4+ T cell counts,
especially among pregnant women initiating lifelong
ART (option B+), will be particularly important. Further
data on using viral load monitoring as a tool to support
adherence among subsets of key populations at risk for
poor follow-up are also needed.

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JDT, CHB, and PE were the lead authors, JDT and RWP
conceptualized the study, JDT and CHB scrutinized
identified studies for eligibility, extracted data and assessed
the methodological quality of included studies. MD,
MP, MA, and RWP provided input on the study design.
All authors critically reviewed the manuscript before
submission.

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Conflicts of interest
None.

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