

# Integrating antiretroviral therapy into antenatal care and maternal and child health settings: a systematic review and meta-analysis

Amitabh B Suthar,<sup>a</sup> David Hoos,<sup>b</sup> Alba Beqiri,<sup>a</sup> Karl Lorenz-Dehne,<sup>c</sup> Craig McClure<sup>d</sup> & Chris Duncombe<sup>e</sup>

**Objective** To determine whether integrating antiretroviral therapy (ART) into antenatal care (ANC) and maternal and child health (MCH) clinics could improve programmatic and patient outcomes.

**Methods** The authors systematically searched PubMed, Embase, African Index Medicus and LiLACS for randomized controlled trials, prospective cohort studies, or retrospective cohort studies comparing outcomes in ANC or MCH clinics that had and had not integrated ART. The outcomes of interest were ART coverage, ART enrolment, ART retention, mortality and transmission of human immunodeficiency virus (HIV).

**Findings** Four studies met the inclusion criteria. All were conducted in ANC clinics. Increased enrolment of pregnant women in ART was observed in ANC clinics that had integrated ART (relative risk, RR: 2.09; 95% confidence interval, CI; 1.78–2.46; *P*: 15%). Increased ART coverage was also noted in such clinics (RR: 1.37; 95% CI: 1.05–1.79; *P*: 83%). Sensitivity analyses revealed a trend for the national prevalence of HIV infection to explain the heterogeneity in the size of the effect of ART integration on ART coverage (*P*=0.13). Retention in ART was similar in ANC clinics with and without ART integration.

**Conclusion** Although few data were available, ART integration in ANC clinics appears to lead to higher rates of ART enrolment and ART coverage. Rates of retention in ART remain similar to those observed in referral-based models.

Abstracts in **عربي**, **中文**, **Français**, **Русский** and **Español** at the end of each article.

## Introduction

In 2009, 49% of pregnant women in low- and middle-income countries did not attend the minimum number of antenatal care (ANC) visits recommended by the World Health Organization (WHO) to prevent or manage the complications of pregnancy and support safe delivery.<sup>1</sup> In addition, 74% were not tested for HIV and 63% of those who tested positive did not receive at least two antiretrovirals, as recommended by WHO, for the prevention of mother-to-child transmission (PMTCT) of HIV.<sup>2,3</sup> Of the infants born to mothers with HIV infection, 85% did not receive a diagnostic HIV test and 65% of those who were infected with HIV did not receive antiretroviral prophylaxis.<sup>2</sup> These service delivery gaps largely account for the fact that an estimated 330 000 infants were born with HIV infection in 2011.<sup>4</sup> Without antiretroviral therapy (ART), most of these children will die before their second birthday.<sup>5</sup>

All 192 Member States of the United Nations have agreed to pursue the Millennium Development Goals (MDGs),<sup>1</sup> which include specific targets related to HIV infection, maternal health and child health to be achieved by 2015. Expanding access to ART in ANC and maternal and child health (MCH) clinics could help achieve universal access to ART (Target 6B), reduce mortality in children less than 5 years old (Target 4A) and reduce the maternal mortality ratio (Target 5A). It could also help to achieve the target, set by WHO<sup>6</sup> and the Joint United Nations Programme on HIV/AIDS, of eliminating vertical HIV transmission by 2015.<sup>7</sup>

The limitations of current service delivery systems are such that people living with HIV often present at health-care

sites with advanced HIV infection, life-threatening opportunistic infections and CD4+ T-lymphocyte counts well below the WHO-recommended eligibility threshold for ART.<sup>8</sup> Delayed diagnosis also keeps people from making important decisions surrounding prevention and care, such as whether to participate in prevention programmes to reduce the risk of HIV transmission, attend family planning services, or start ART, cotrimoxazole prophylaxis or isoniazid preventive therapy. As part of the Treatment 2.0 initiative, WHO is focusing on providing guidance on the integration of HIV service delivery systems with other health-care services, the decentralization of these systems to the community level, and the achievement of earlier diagnosis linked with prevention, care and treatment services.<sup>9</sup>

WHO currently recommends ART for pregnant women with CD4+ lymphocyte counts  $\leq 350$  cells/ $\mu$ L.<sup>10</sup> For women with CD4+ lymphocyte counts  $> 350$  cells/ $\mu$ L, WHO recommends triple antiretroviral prophylaxis as one of two options, although practice is shifting towards lifelong ART for all HIV-positive pregnant women. The advantages of lifelong ART for all HIV-positive pregnant women are: (i) likely benefits to the women's own health; (ii) prevention of HIV transmission during subsequent pregnancies; (iii) prevention of transmission to HIV-negative partners; (iv) delivery of a consistent message to communities that ART, once started, should be continued for life; and (v) simpler service delivery by eliminating the need for periodic CD4+ T-lymphocyte counts to know when to start, suspend and re-initiate ART (although CD4+ lymphocyte counts or viral load assays are still desirable for determining baseline immunological status and monitoring response to

<sup>a</sup> Department of HIV/AIDS, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland.

<sup>b</sup> Mailman School of Public Health, Columbia University, New York, United States of America (USA).

<sup>c</sup> Technical and Operations Support Department, Joint United Nations Programme on HIV/AIDS, Geneva, Switzerland.

<sup>d</sup> HIV/AIDS Programme Division, United Nations Children's Fund, New York, USA.

<sup>e</sup> Global Health Programme, Bill & Melinda Gates Foundation, Seattle, USA.

Correspondence to Amitabh B Suthar (e-mail: amitabh.suthar@gmail.com).

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treatment).<sup>11</sup> In the United States and Europe, vertical HIV transmission has been largely eliminated owing to the scale-up of ART and triple antiretroviral prophylaxis.<sup>12,13</sup> Regardless of PMTCT strategy, WHO recommends providing antiretroviral prophylaxis to children exposed to HIV during breastfeeding, and ART to all children less than 2 years of age with confirmed HIV infection.<sup>10</sup>

In countries with generalized HIV epidemics (i.e. with an antenatal HIV prevalence > 1%), WHO recommends provider-initiated testing and counseling in all health facilities.<sup>14</sup> The recommendation includes all pregnant women attending ANC and MCH clinics. While these clinics often provide antiretroviral prophylaxis for PMTCT, women and infants who need ART are often referred to specialized HIV clinics in another area of the facility or in another facility altogether. Attending specialized HIV clinics in addition to ANC or MCH services can increase transportation costs, make people miss work and neglect other obligations and be perceived as stigmatizing. Because of these reasons, some pregnant women do not attend specialized HIV clinics and are lost to care or fail to receive ART, even if they are eligible.<sup>15</sup> Moreover, large numbers of infants are exposed to and infected with HIV because of poor integration of ANC and HIV services and inadequate access to HIV care. Not offering these services in an integrated fashion also leads to high rates of attrition, delayed diagnosis of paediatric HIV infection and paediatric HIV-related mortality.<sup>2,16</sup> Providing ART in ANC and MCH clinics to eligible pregnant women and infants offers a continuum of care at a single site.<sup>11</sup> The impact of integrating PMTCT services with other health services has been studied,<sup>17,18</sup> but there has not been a systematic review or synthesis of the evidence surrounding the effect of integrating ART with ANC and MCH clinics on programmatic and patient outcomes. The objective of this study is to review this evidence and summarize it through meta-analyses.

## Methods

We registered the protocol of this systematic review with the International Prospective Register of Systematic Reviews (identification number: CRD42011001403) in June 2011, and we conducted the review in accor-

### Box 1. Strategy used to conduct systematic search of studies on integration of antiretroviral therapy in antenatal care and maternal and child health clinics

#### Search no. and term(s) used

1. HIV
2. AIDS
3. HIV or AIDS
4. Antenatal
5. ANC
6. Maternal and child
7. MCH
8. antenatal or ANC or maternal and child or MCH
9. Preventing mother to child transmission
10. PMTCT
11. MTCT
12. Antiretroviral therapy
13. ART
14. HAART
15. cART
16. Antiretroviral
17. ARV
18. Preventing mother to child transmission or PMTCT or MTCT or antiretroviral therapy or ART or HAART or cART or antiretroviral or ARV
19. [HIV or AIDS] and [antenatal or ANC or maternal and child or MCH] and [preventing mother to child transmission or PMTCT or MTCT or antiretroviral therapy or ART or HAART or cART or antiretroviral or ARV]

Note: The same search strategy was used to search PubMed, Embase, LILACS and African Index Medicus. (Embase covers from 1974 to the present and PubMed, from 1966 to the present.) The search was conducted in successive steps from 1 to 19.

dance with PRISMA guidelines.<sup>19,20</sup> We searched PubMed, Embase, African Index Medicus and the Latin American and Caribbean Health Science Literature (LILACS) databases without restriction of language or publication date.

A librarian helped us to develop a search strategy for identifying all randomized controlled trials, prospective cohort studies and retrospective cohort studies on the effect of integrating ART into either ANC or MCH clinics (Box 1). Studies were included if the study population was composed of people living with HIV, the intervention was a self-identified ANC or MCH clinic that had integrated ART (i.e. that provided ART as part of its routine services), the comparator was a self-identified ANC or MCH clinic that had not integrated ART (i.e. that did not provide ART), and the outcome was ART coverage among women eligible for ART according to national clinical guidelines. We also included studies that assessed enrolment in ART, retention in ART, mortality or HIV transmission. The intervention criterion was not based upon specific programmatic modalities for the provision of ART as part of routine

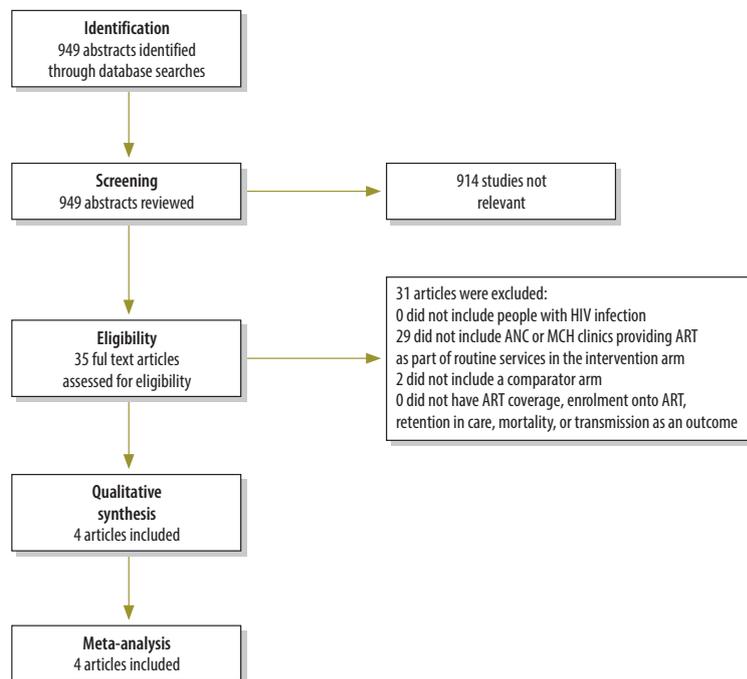
services. ABS searched the Cochrane Central Register of Controlled Trials, the International Standard Randomized Controlled Trial Number Register and ClinicalTrials.gov for future and on-going studies and contacted experts in the field to identify on-going studies or unpublished research.

Two of the investigators (ABS and AB) reviewed the abstracts of all articles identified. The full texts of all articles selected by either investigator were matched against the inclusion criteria and studies not meeting these criteria were excluded (Fig. 1). Disagreements on whether a given article met the inclusion criteria were resolved through discussion. We extracted the data using a standardized spreadsheet that was created when the review protocol was prepared. The spreadsheet collected information on the first author, year of publication, methods and design, study population, intervention and control arms, duration of follow-up, inclusion and exclusion criteria, outcomes, and losses to follow up.

## Statistical analyses

To assess publication bias we created a funnel plot with effect measures on the

Fig. 1. Flow diagram showing study selection in systematic review of studies on the integration of antiretroviral therapy (ART) into maternal and child health (MCH) services



ANC, antenatal care; HIV, human immunodeficiency virus.

*x*-axis and the standard errors of the logarithm (log) of the effect measures on the *y*-axis. To test the funnel plot's symmetry and assess publication bias we used the Egger and Begg tests. Since studies that explored ART coverage and ART enrolment as outcomes were similar enough with respect to other inclusion criteria to combine, we performed a meta-analysis of the studies. Coverage and enrolment were expressed as proportions and their frequency was quantified in terms of risk. For sensitivity analyses we used the natural log of the relative risks (RRs) and its standard error.<sup>21</sup> The use of  $\chi^2$  and  $\tau^2$  statistics for assessing heterogeneity in effect size across studies requires that the number of events in each study arm be known. Since these data were not available for all studies meeting the inclusion criteria, an  $I^2$  statistic was used to measure heterogeneity.  $I^2$  statistics are calculated by subtracting the degrees of freedom from the  $Q$  statistic and dividing the resulting number by the  $Q$  statistic.<sup>22</sup>  $I^2$  values less than 25% indicate low heterogeneity; values near 50% indicate moderate heterogeneity and those above 75% indicate high heterogeneity.<sup>23</sup> When heterogeneity was  $\geq 25\%$  we used

random-effects models; when it was  $< 25\%$  we used fixed-effects models.<sup>24</sup> We performed sensitivity analyses to explore the potential causes of heterogeneity, including differences in the national prevalence of HIV infection<sup>25</sup> and in national ANC coverage.<sup>26</sup> Since reported or estimated effect sizes were included when calculating the summary RRs, we did not need to control for missing data. We used STATA version 10.0 to conduct all analyses.

## Results

### Search results

Of the 949 abstracts identified through the database searches, 914 were irrelevant. The remaining 35 full text articles were assessed for eligibility: 29 were excluded because the study's intervention did not meet the definition used in this review; 2 more studies<sup>27,28</sup> were excluded because they lacked a comparator arm (Fig. 1). Four studies met the inclusion criteria (Table 1); three of them reported on ART enrolment<sup>30–32</sup> and all four reported on ART coverage.<sup>29–32</sup> All studies were conducted in self-identified ANC clinics; none was conducted in a self-identified MCH clinic. One study was a

prospective cohort study<sup>30</sup> and the other three were retrospective cohort studies.<sup>29,31,32</sup> Moreover, no studies meeting eligibility criteria were found by contacting experts or by searching the Cochrane Central Register of Controlled Trials, the International Standard Randomized Controlled Trial Number Register, or the reference lists of studies meeting inclusion criteria. One on-going study was found on ClinicalTrials.gov.<sup>33</sup> This was a cluster-randomized trial in 12 ANC clinics randomly assigned to integration or non-integration of HIV care and ART. It had approximately 1200 participants and the primary outcome was vertical HIV transmission. Follow-up of participants is expected to end in 2012.

### Study results

The proportion of pregnant women who enrolled in ART was consistently higher in ANC clinics that had integrated ART (Mozambique, RR: 2.53; 95% CI: 1.88–3.40; Rwanda, RR: 1.90; 95% CI: 1.50–2.30; Zambia, adjusted odds ratio (OR): 2.06; 95% CI: 1.27–3.34).<sup>30–32</sup>

The proportion of eligible pregnant women receiving ART was also higher in ANC clinics that had integrated ART (Mozambique, RR: 1.58; 95% CI: 1.17–2.14; Jamaica, RR: 1.38; 95% CI: 1.29–1.47; Zambia, OR: 2.01; 95% CI: 1.37–2.95).<sup>29–31</sup> In Rwanda, ART coverage was not significantly higher in ANCs clinics that had integrated ART (RR: 0.90; 95% CI: 0.70–1.10).<sup>32</sup>

In one of the included studies, ART retention after 90 days was 87.8% (244/278) in the ANC clinics that had integrated ART and 91.3% (94/103) in the referral HIV clinics for pregnant women on ART.<sup>30</sup> The investigators reported no statistical differences in retention at the individual or cluster level.<sup>30</sup>

### Meta-analyses

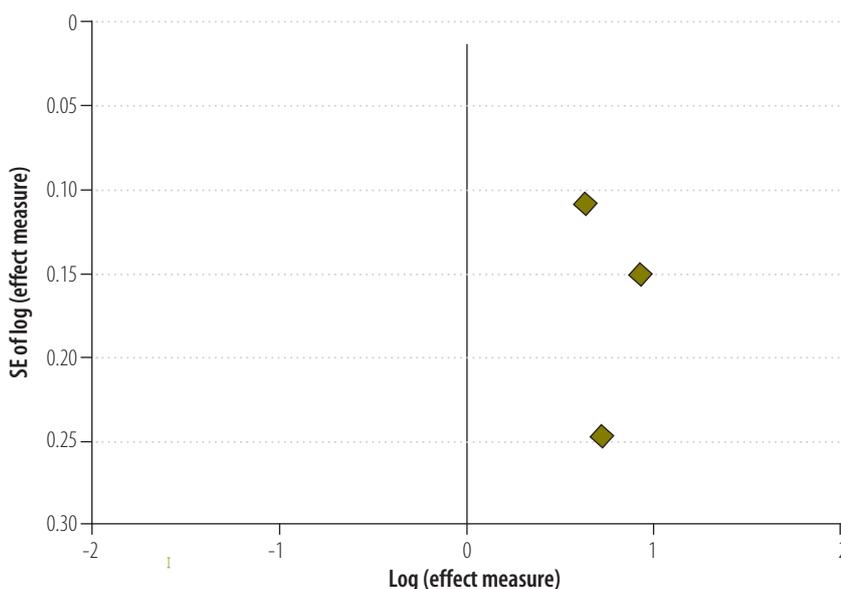
The fewer the studies included in a meta-analysis, the lower the power to detect publication bias.<sup>34</sup> Because few studies on ART enrolment were included in our meta-analysis, the power to detect such bias was low. With this caveat, the  $P$ -values for the Begg and Egger tests (0.60 and 0.56, respectively) suggested no publication bias for this outcome (Fig. 2). The  $I^2$  statistic for enrolment in ART was 15%, which suggests low heterogeneity in effect size.<sup>23</sup> We noted significantly higher enrolment in ANC clinics that had integrated ART than in those that had not (RR: 2.09; 95% CI:

Table 1. **Studies that met inclusion criteria in systematic review of the literature on the integration of antiretroviral therapy (ART) into maternal and child health services**

Author (year)	Population	Intervention	Comparator	Providers initiating ART	Losses to follow-up	Variables included in study model
Christie (2008) <sup>29</sup>	351 Jamaican women attending ANC clinics in Kingston, St Andrew and St Catherine, Jamaica	(i) Leadership, mentoring and training to health-care workers; (ii) implementing unified programme for the PMTCT of HIV infection; (iii) establishing unified maternal and infant treatment and care programme; (iv) building outcomes-based research agenda; (v) expanding programme	Intervention progress was measured over 5 years	Not reported	Not reported	None
Killam (2010) <sup>30</sup>	31 536 Zambian women attending eight public sector clinics in Lusaka district, Zambia	ART was provided in the ANC clinic to eligible women	ART-eligible women were referred urgently to an ART clinic located on the same premises as the ANC clinic but physically separate and separately staffed	Clinical officer (undefined)	10.8% in intervention arm; 6.8% in the comparator arm	Clinic site cluster and time effects
Pfeiffer (2010) <sup>31</sup>	ART was integrated and decentralized into 67 Mozambique health-care sites, including ANC clinics	(i) Location of different services within the same facility; (ii) training of staff to provide multiple services; (iii) provision of tools, processes and training to better link separate services; (iv) strengthening of linkages, referral and follow-up between facility levels; (v) harmonization of logistics systems	From 2001–2005 Mozambique used a vertical day hospital model in which new, freestanding HIV treatment hospitals were constructed in large population centres alongside existing hospital compounds	ART providers (undefined)	70% in comparator arm; 25% in intervention arm	None
Tsague <sup>32</sup> (2010)	938 pregnant women received care at 18 full package sites and the 14 stand-alone sites in Rwanda	Full package sites provided PMTCT and ART services at the same site	Stand-alone sites referred ART-eligible women to the nearest ART site	Physicians	Not reported	None

ANC, antenatal care; ART, antiretroviral therapy; HIV, human immunodeficiency virus; PMTCT, prevention of mother-to-child transmission.

Fig. 2. **Funnel plot for studies meeting inclusion criteria for antiretroviral therapy (ART) enrolment outcome**

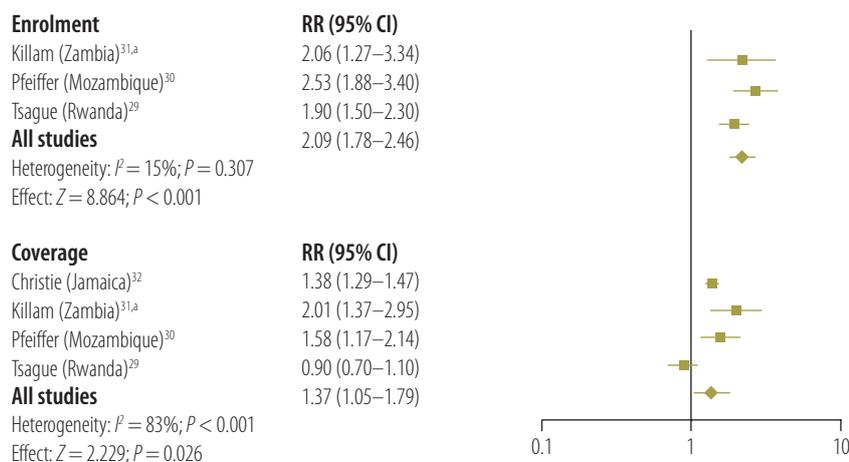


SE, standard error.  
Egger and Begg's test *P*-values for publication bias were 0.56 and 0.60, respectively.

1.78–2.46; *P* for effect: < 0.001; *P* for heterogeneity: 0.307; Fig. 3).

The power to detect publication bias was also low for the coverage outcome. Nonetheless, the *P*-values for the Begg and Egger tests (0.73 and 0.65, respectively) suggested the absence of publication bias (Fig. 4). Since the *I*<sup>2</sup> statistic for ART coverage was 84%, the heterogeneity in effect size was judged to be high.<sup>23</sup> A sensitivity analysis of national HIV infection prevalence suggested a trend towards it being predictive of the heterogeneity (*P* = 0.13).<sup>25</sup> A sensitivity analysis of national ANC coverage<sup>26</sup> – i.e. of the percentage of pregnant women who made at least one ANC clinic visit – suggested that it was not a meaningful predictor of heterogeneity (*P* = 0.32). ART coverage was significantly higher in ANC clinics that had integrated ART than in those that had not (RR: 1.37; 95% CI: 1.05–1.79; *P* for effect size = 0.026; *P* for heterogeneity < 0.001; Fig. 3).

Fig. 3. **Enrolment in and coverage with antiretroviral therapy (ART) among pregnant women attending an antenatal care clinic that had integrated ART**

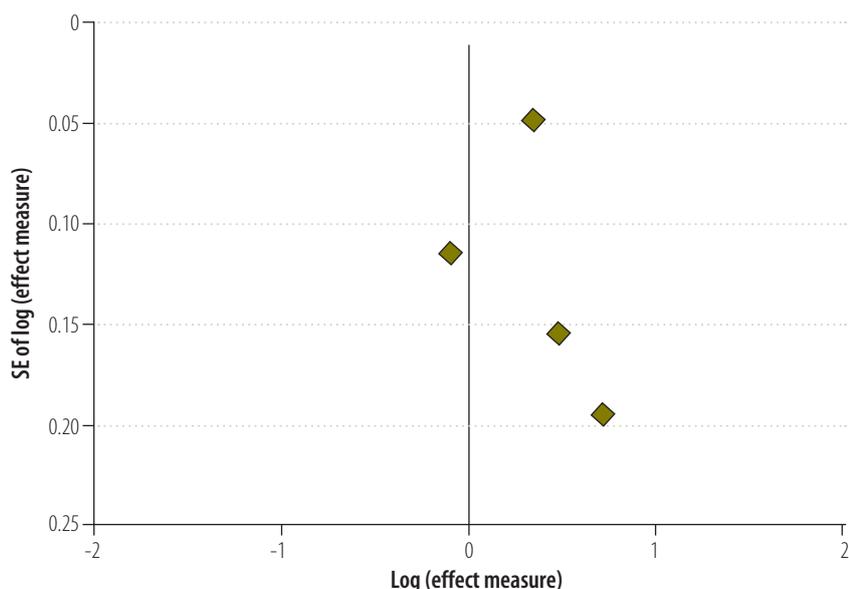


CI, confidence interval; RR, relative risk.

The centres of the squares represent the study estimates; the centres of the quadrilaterals represent summary estimates; the horizontal lines represent 95% confidence intervals.

<sup>a</sup> Indicates that the effect estimate in the study is an odds ratio.

Fig. 4. **Funnel plot for studies meeting inclusion criteria for coverage outcome**



SE, standard error.

Egger and Begg's test  $P$ -values for publication bias were 0.65 and 0.73, respectively.

## Discussion

This systematic review shows that enrolment in ART among pregnant women and coverage with ART among those pregnant women who were eligible for treatment were higher in clinics that had integrated ART than in those that had not. To understand the generalizability of these findings it is important to examine why ART was integrated into the ANC clinics included in these studies. In Mozambique this was done in

provinces with a high prevalence of HIV infection.<sup>31</sup> Zambia implemented ART integration in the clinics with the largest volumes of HIV-positive pregnant women.<sup>30</sup> Similarly, Jamaica integrated ART into clinics in high-prevalence communities.<sup>29</sup> Tsague et al. did not explain why clinics in the Western province and Kigali were chosen in Rwanda,<sup>32</sup> but most programmes appear to have integrated ART into ANC clinics located in the areas with the largest populations of HIV-positive pregnant women.

One limitation of this review was that studies were eligible for inclusion only if they defined integration as the provision of ART in ANC or MCH clinics as part of routine services. Other models of integration could also lead to increased enrolment in, and coverage with, ART and these models should be reviewed by countries considering integration.<sup>35–37</sup> For example, one model might be to offer integrated services one day of the week rather than daily as part of routine services. Another limitation is that most included studies relied on abstracting clinic data, which may have introduced measurement bias. Furthermore, results from randomized controlled trials were not available; all findings were generated by prospective and retrospective cohort studies, which tend to be more vulnerable to unmeasured selection bias, measurement bias and confounding than cluster-randomized trials. We excluded studies without a comparator arm,<sup>27,28</sup> but descriptive studies can also provide important lessons on feasibility and best practices. Finally, the decision to provide ART in ANC clinics must be made by both MCH and HIV programmes. The studies that met our inclusion criteria presented HIV-related outcomes, but understanding the effects of service integration on MCH outcomes is also important. According to one recent study, integration may increase postnatal follow-up for childhood vaccinations and HIV antibody testing.<sup>38</sup> Nonetheless, further research on how service integration affects the quality of family planning services, antenatal care, postnatal care and infant care is needed.

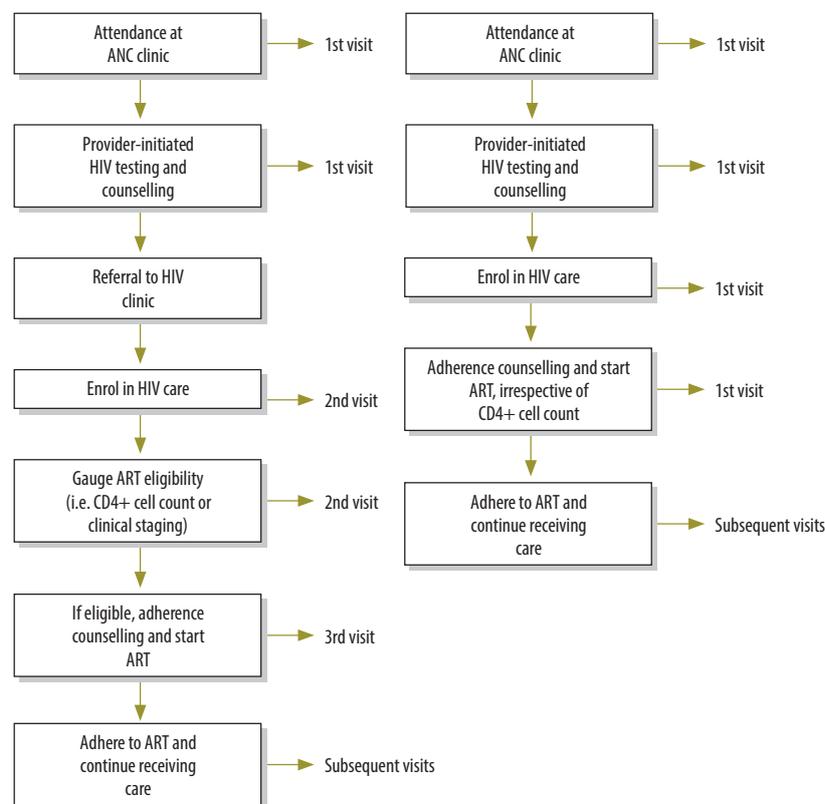
Low ART coverage among pregnant women has been attributed to several factors: complicated prophylaxis and treatment algorithms; complex referral systems; HIV test stock-outs; antiretroviral stock-outs; staff shortages in HIV services; late payment of lay counselors (leading to absenteeism) and slow processing of CD4+ T-lymphocyte test results.<sup>39</sup> Furthermore, in qualitative studies from Malawi,<sup>40</sup> Uganda,<sup>41</sup> and Zimbabwe<sup>42</sup> that examined the reasons for losses to follow-up, the main drivers were found to be the following: long queues at HIV clinics; the cost of transport from homes to clinics; fear of disclosure of HIV status; lack of support from partners who did not want to be tested for HIV; and suggestions on the part of staff to not breastfeed their babies

and to feed them formula instead (which was a social taboo). Many of these problems could be alleviated by integrating ART into ANC clinics. In a recent study, women were found to have had positive experiences in integrated ANC clinics. They reported that staff had treated them well and given them helpful counselling and that their babies had received good care and were free from HIV infection because of this.<sup>38</sup> The overall acceptability of receiving ART in ANC clinics from the women's perspective should continue to be studied closely.

In the on-going trial,<sup>33</sup> a qualitative component explored the operational feasibility of integrating ART and the acceptability of integration to health-care staff in ANC clinics.<sup>43</sup> Providers felt that integration increased efficiency, decreased the time spent by patients in clinics, improved provider-patient relationships, and improved ART adherence because of decreased stigma and increased confidentiality. All of these factors increased patient satisfaction and may have contributed to improved quality of care. Providers also felt that clinics needed to ensure the presence of enough staff to cope with the additional workload created by integrating HIV services. Ensuring sufficient staff may require shifting ART initiation and maintenance from physicians to nurses and midwives and engaging additional community health workers to perform HIV testing and counselling, ART adherence counselling and simple clinic tasks. Providers also noted that integration decreased the work associated with referrals and simplified recordkeeping because patient records were kept in only one place.

The risk of vertical HIV transmission and the chances of achieving viral load suppression depend on the duration of ART. For each additional week of ART, the odds of transmission decrease by 8 to 14%.<sup>44,45</sup> Indeed, in an integrated South African ANC clinic, fewer than 1% of the women who had been on ART for at least 7 weeks during pregnancy transmitted HIV to their infants.<sup>28</sup> Therefore, optimizing service delivery by minimizing the number of clinic visits and the number of weeks that transpire before initiating ART could reduce losses to care and the risk of vertical HIV transmission. Although the process for delivering ART to eligible pregnant women varies, it generally involves: (i) attendance at an

Fig. 5. **Antiretroviral therapy (ART) for pregnant women under a referral-based model with current eligibility criteria (left) and under a service delivery model using universal ART eligibility criteria in integrated antenatal care (ANC) clinics (right)**



ART, antiretroviral therapy; HIV, human immunodeficiency virus.

In both models infants should be given daily nevirapine syrup until they are 6 weeks of age.<sup>10</sup>

ANC clinic; (ii) provider-initiated HIV testing and counselling; (iii) referral to an HIV clinic; (iv) enrolment in care at the HIV clinic; (v) assessment of eligibility for ART (based on CD4+ T-lymphocyte count and/or WHO clinical stage); (vi) initiation of ART if eligible, and (vii) maintaining high adherence to ART and life-long retention in HIV treatment and care (Fig. 5). The chances that a pregnant woman will not be retained in care increases with every additional clinic visit that she has to attend before receiving ART. According to studies from four African countries, 30 to 83% of pregnant women were not retained in care during referral from ANC to HIV clinics.<sup>46-49</sup> In Malawi, 71% of infants were not retained in care during referral from ANC to HIV clinics.<sup>50</sup> Integrating ART into ANC clinics would prevent these losses and may make it possible for programmes to increase ART coverage in pregnant women and infants. For ART coverage to be maximized, however, women will

need to attend ANC clinics earlier in pregnancy. Although it is beyond the scope of this review, this issue is very important and has direct bearing on MDG 4 (reduce child mortality), MDG 5 (improve maternal health), MDG 6 (increase proportion of population with access to ART), and the elimination of paediatric HIV infection.<sup>51</sup>

Poor retention in care among women who are initiated on ART in ANC clinics is a legitimate concern. Only one study in this review assessed ART retention. It revealed no statistically significant differences in retention three months after ART initiation between pregnant women who had been initiated on ART at ANC clinics or at HIV clinics.<sup>30</sup> In another systematic review, retention on ART in HIV clinics was 77% after 12 months.<sup>52</sup> Similarly, in Malawi and Zambia, where ART was provided to all pregnant women who are HIV-positive, retention was 83% after 6 months and 77% after 12 months, respectively.<sup>53,54</sup>

Most antenatal care clinics lack the capacity to perform CD4+ T-lymphocyte counts, but when WHO clinical staging criteria are used to gauge ART eligibility, many eligible women who are asymptomatic remain undetected.<sup>55</sup> Moreover, clinics with the capacity to perform these counts risk losing 21 to 57% of the eligible pregnant women while waiting for test results.<sup>46–49</sup> Providing ART only during pregnancy and breast-feeding is an option in women who are not eligible for ART per national criteria; however, in countries where women have high parity rates – e.g. in Malawi, where the fertility rate is 5.7 children per woman<sup>56</sup> – stopping and starting ART may be operationally difficult, increase the hazard of death or progression to AIDS,<sup>57</sup> increase the risk of HIV transmission and select for antiretroviral resistance mutations.<sup>58</sup> Indeed, in one study vertical HIV transmission was observed in 0.7% of the women who initiated ART before becoming pregnant and in 5.7% of the women who started ART during pregnancy.<sup>44</sup> Given the health and prevention benefits of lifelong ART in pregnant women, some have argued that programmes should initiate ART immediately after a woman tests positive.<sup>59–61</sup> Some countries are responding to this call. Malawi provides lifelong ART to all pregnant women with HIV infection, regardless of their CD4+ T-lymphocyte counts.<sup>62</sup> Although the results of this approach are still under study, the available data appear promising. According to data from Malawi collected 2 months after birth, of 628 infants who were tested for HIV infection with polymerase chain reaction (PCR), 11 (1.75%) had a positive result.<sup>53</sup> Moreover, data available for all infants at two months of age – irrespective of the availability of a PCR result – showed that 8 of the 4606 infants (0.17%) had died.<sup>53</sup> Data collected on 130 infants in Zambia 12 months after birth showed that 1 infant (0.8%) was positive for HIV and that 5 infants (3.8%) had died.<sup>54</sup>

Integrating ART into ANC clinics may involve resolving several operational issues. Nurses and midwives will need to be trained to provide HIV care and

ART. After the training, they will have to be adequately supervised to ensure that the HIV care delivered is of high quality. To avoid overburdening nurses and midwives, other cadres of health workers may have to share some of their tasks. Moreover, in clinics where provider-initiated testing and counselling has not been implemented, it might also be necessary to train nurses and midwives, in addition to pharmacy technologists and community health workers, to provide HIV testing and counselling. Programmes for the care of people with HIV infection may need to improve supply chain management systems to prevent shortages or surpluses of HIV tests and antiretroviral fixed-dose combinations.<sup>63</sup> To be effective, integration will have to be underpinned by (i) shared ownership by maternal and child health programmes as well as HIV programmes, (ii) excellent communication with other clinics and strong referral systems, and (iii) systematic and – where feasible – electronic monitoring and evaluation of ART.<sup>64</sup> Programmes must also decide whether to refer women out of ANC clinics and, if they do so, when and how to do it. Some countries have decided to postpone referral until after children have completed their immunizations to avoid referring their mothers back and forth between the HIV and ANC clinics during subsequent pregnancies. In one of the studies identified, ART initiation rates were similar in ANC clinics that did and did not offer ART.<sup>32</sup> This may be because the ANC clinics that did not offer ART had systems for escorting women to HIV services, offered psychosocial support services and used social workers to track women who missed appointments.<sup>32</sup> Integrating ART into antenatal care clinics may not result in higher ART initiation rates in ANC clinics offering this type of care.

When pregnant women initiate ART in early pregnancy, they may feel pressured to disclose their HIV status because others, including their partners, might find out that they are taking antiretrovirals. To avoid this, ANC clinics can offer pregnant women couples testing and counselling for HIV

infection at their first antenatal visit. WHO recommends this as a key intervention to enable couples to disclose their HIV status to each other and make informed decisions surrounding HIV prevention and reproduction, including family planning.<sup>65</sup> To increase male participation in couples testing and counselling in ANC clinics, men could be sent invitation letters<sup>66</sup> or offered HIV testing and counselling in nearby community sites linked to care (e.g. churches or bars).<sup>67</sup>

In conclusion, the available data suggest that integrating ART into ANC clinics is feasible and improves ART coverage. Further research is needed to determine ART integration's overall effects on health systems, its feasibility over the long term and barriers to its implementation, such as a large volume of cumulative enrolment. As HIV and MCH programmes consider whether to integrate ART into maternal and child health settings, they should closely examine operational issues, administrative processes and disease burden at the clinic level to determine the best way of expanding access to ART. ■

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## ملخص

## دمج العلاج بمضادات الفيروسات القهقرية في مواقع الرعاية السابقة للولادة وصحة الأم والطفل: استعراض منهجي وتحليل وصفي

فاصل الثقة 95٪: من 1.78 إلى 2.46؛ إحصاء  $I^2$ : 15٪). ولوحظت أيضاً زيادة في تغطية العلاج بمضادات الفيروسات القهقرية في هذه العيادات (الاختطار النسبي: 1.37؛ فاصل الثقة 95٪: من 1.05 إلى 1.79؛ إحصاء  $I^2$ : 83٪). وأظهرت تحليلات الحساسية اتجاهها لانتشار عدوى فيروس العوز المناعي البشري على الصعيد الوطني بغيّة توضيح التغايرية في حجم تأثير دمج العلاج بمضادات الفيروسات القهقرية على تغطية العلاج بمضادات الفيروسات القهقرية (الاحتمال=0.13). وتشابه الإبقاء في العلاج بمضادات الفيروسات القهقرية في عيادات الرعاية السابقة للولادة التي دمجت أو لم تدمج العلاج بمضادات الفيروسات القهقرية.

الاستنتاج على الرغم من قلة البيانات المتاحة، يبدو أن دمج العلاج بمضادات الفيروسات القهقرية في عيادات الرعاية السابقة للولادة سيؤدي إلى ارتفاع معدلات التسجيل في العلاج بمضادات الفيروسات القهقرية وتغطيته. وتظل معدلات الإبقاء في العلاج بمضادات الفيروسات القهقرية مشابهة لتلك التي لوحظت في النماذج المستندة على الإحالة.

الغرض تحديد ما إذا كان دمج العلاج بمضادات الفيروسات القهقرية في عيادات الرعاية السابقة للولادة وصحة الأم والطفل سيؤدي إلى تحسين الحاصلات البرمجية وحاصلات المرضى. الطريقة قام المؤلفون بإجراء بحث منهجي في قواعد بيانات PubMed و Embase و African Index Medicus و LiLACS بخصوص التجارب العشوائية التي أجريت في بيئة مراقبة أو الدراسات الأترابية الاستطلاعية أو الدراسات الأترابية الاستعدادية لمقارنة الحاصلات في عيادات الرعاية السابقة للولادة أو صحة الأم والطفل التي دمجت ولم تدمج العلاج بمضادات الفيروسات القهقرية. وكانت الحاصلات المهمة هي تغطية العلاج بمضادات الفيروسات القهقرية والتسجيل في العلاج بمضادات الفيروسات القهقرية وإبقاء العلاج بمضادات الفيروسات القهقرية ومعدل الوفيات وانتقال فيروس العوز المناعي البشري (HIV).

النتائج حققت أربع دراسات معايير الإدراج. وقد أجريت جميعها في عيادات الرعاية السابقة للولادة. ولوحظت زيادة في تسجيل السيدات الحوامل في العلاج بمضادات الفيروسات القهقرية في عيادات الرعاية السابقة للولادة التي دمجت العلاج بمضادات الفيروسات القهقرية (الاختطار النسبي: 2.09؛

## 摘要

**抗逆转录病毒疗法纳入产前护理和母婴保健诊所:** 目的 确定将抗逆转录病毒疗法 (ART) 纳入产前护理 (ANC) 和母婴保健 (MCH) 诊所是否可以改善规范化患者治疗效果。

**方法** 作者系统检索PubMed、Embase、非洲医学引文索引和LiLACS进行随机对照试验、前瞻性队列研究或者回顾性队列研究，比较纳入ART和没有纳入ART的ANC或MCH诊所的效果。关注的效果是ART覆盖范围、ART招募、ART保持、艾滋病毒 (HIV) 的死亡率和传播。

**结果** 有四项研究符合纳入标准。所有研究都在ANC诊所执行。在纳入ART的ANC诊所内观察到孕妇ART入组增加

## 系统综述和荟萃分析

(相对风险, RR: 2.09; 95% 置信区间, CI: 1.78-2.46;  $I^2$ : 15%)。这些诊所中还注意到ART覆盖范围的增加 (RR: 1.37; 95% CI: 1.05-1.79;  $I^2$ : 83%)。敏感性分析显示出艾滋病毒感染患病率的全国趋势，解释了在ART覆盖范围方面ART整合效果的大小的异质性 ( $P=0.13$ )。纳入和不纳入ART的ANC诊所在ART保持方面相似。

**结论** 虽然可用的数据很少，在ANC诊所中纳入ART仍显示出会产生更高的ART入组和ART覆盖率。在基于转介的模型中观察到的ART保持相似。

## Résumé

## Intégration de la thérapie antirétrovirale dans les établissements de soins prénataux et de santé maternelle et infantile: revue systématique et méta-analyse

**Objectif** Déterminer si l'intégration de la thérapie antirétrovirale (TAR) dans les établissements de soins prénataux (ESP) et de santé maternelle et infantile (SMI) pourrait améliorer les résultats du programme et la santé du patient.

**Méthodes** Les auteurs ont systématiquement recherché via PubMed, Embase, African Index Medicus et LILACS des essais contrôlés randomisés, des études de cohorte prospectives et des études de cohorte rétrospectives comparant les résultats des cliniques ESP ou SMI ayant ou n'ayant pas intégré la TAR. Les résultats pris en compte comprenaient la couverture, la participation et la rétention de la TAR, ainsi que la mortalité et la transmission du virus d'immunodéficience humaine (VIH).

**Résultats** Quatre études répondaient aux critères d'inclusion. Toutes ont été menées dans des cliniques ESP. Une participation accrue des

femmes enceintes à la TAR a été observée dans les cliniques ESP qui l'avaient intégrée (risque relatif, RR: 2,09; intervalle de confiance IC à 95%: 1,78 à 2,46;  $I^2$ : 15%). Une couverture plus importante de la TAR a également été notée dans ces cliniques (RR: 1,37; IC à 95%: 1,05 à 1,79;  $I^2$ : 83%). Les analyses de sensibilité ont révélé une tendance à la prévalence nationale de l'infection par le VIH pour expliquer l'hétérogénéité de la taille de l'effet de l'intégration de la TAR sur sa couverture ( $P=0,13$ ). La rétention de la TAR était similaire dans les cliniques ESP avec ou sans intégration de la TAR.

**Conclusion** Bien que peu de données aient été disponibles, l'intégration de la TAR dans les cliniques ESP semblait entraîner une augmentation des taux de participation et de couverture de la TAR. Les taux de rétention de la TAR restent semblables à ceux qui sont observés dans les modèles de référence.

## Резюме

### Интеграция антиретровирусной терапии в условиях дородового наблюдения и охраны здоровья матери и ребенка: систематический обзор и мета-анализ

**Цель** Определить, может ли интеграция антиретровирусной терапии (АРТ) в клиниках дородовой помощи (ДРП) и клиниках охраны здоровья матери и ребенка (ОЗМиР) содействовать достижению программных целей и улучшить результаты лечения пациентов.

**Методы** Авторы выполняли систематический поиск в базах данных PubMed, Embase, African Index Medicus и LiLACS результатов рандомизированных контролируемых испытаний, проспективных и ретроспективных когортных исследований, сравнивая результаты в клиниках ДРП или ОЗМиР, в которых проводилась и не проводилась интеграция АРТ. К числу результатов, представляющих интерес, относился охват АРТ, прием на АРТ, ретенция АРТ, смертность и передача вируса иммунодефицита человека (ВИЧ).

**Результаты** Четыре исследования соответствовали критериям включения. Все они были проведены в клиниках ДРП. Увеличение

числа беременных женщин, вовлеченных в АРТ, наблюдается в клиниках ДРП, которые осуществили интеграцию АРТ (относительный риск, ОР: 2,09; 95% доверительный интервал (ДИ) – 1,78–2,46;  $I^2$ : 15%). Увеличение охвата АРТ было также отмечено в данных клиниках (ОР: 1,37; 95% ДИ: 1,05–1,79;  $I^2$ : 83%). Анализы чувствительности показали, что тенденцию к распространению на национальном уровне ВИЧ-инфекции объясняет неоднородность влияния эффекта интеграции АРТ на охват АРТ ( $P=0,13$ ). Ретенция АРТ была одинаковой в клиниках ДРП как с интегрированной АРТ, так и без нее.

**Вывод** Хотя количество имеющихся данных было невелико, интеграция АРТ в клиниках ДРП, похоже, ведет к росту числа приемов на АРТ и охвата АРТ. Темпы ретенции АРТ остаются аналогичными тем, которые наблюдаются в моделях, в которых используется направление к врачу-специалисту.

## Resumen

### Integración del tratamiento antirretroviral en los centros de atención prenatal y salud materno-infantil: examen sistemático y metaanálisis.

**Objetivo** Determinar si la integración del tratamiento antirretroviral (TAR) en la atención prenatal (APN) y la salud materno-infantil (SMI) podría mejorar los resultados programáticos y del paciente.

**Métodos** Partiendo de las bases de datos PubMed, Embase, Index Medicus de la Región de África y LiLACS, los autores realizaron búsquedas sistemáticas de ensayos controlados aleatorizados, estudios de cohortes prospectivos o estudios de cohortes retrospectivos en los que se compararon los resultados en clínicas de APN o SMI que habían y que no habían integrado el TAR. Los resultados de interés fueron la cobertura del TAR, la inclusión en el TAR, la retención en el TAR, la mortalidad y la transmisión del virus de la inmunodeficiencia humana (VIH).

**Resultados** Cuatro estudios cumplieron los criterios de inclusión. Todos ellos se realizaron en clínicas de APN. Se observó un aumento de la inclusión de mujeres embarazadas en el TAR en aquellas clínicas de

APN que se habían integrado el TAR (riesgo relativo, RR: 2,09, intervalo de confianza del 95%, IC: 1,78–2,46;  $I^2$ : 15%). En estas clínicas también se observó un aumento de la cobertura del TAR (RR: 1,37; IC del 95%: 1,05–1,79;  $I^2$ : 83%). Los análisis de sensibilidad revelaron una tendencia en la prevalencia nacional de la infección por el VIH para explicar la heterogeneidad en la magnitud del efecto de la integración del TAR sobre la cobertura del TAR ( $P=0,13$ ). La retención en el TAR fue similar en las clínicas de APN con y sin integración del TAR.

**Conclusión** A pesar de la escasez de los datos disponibles, la integración del TAR en las clínicas de APN parece traducirse en mayores tasas de inclusión en el TAR y de cobertura del TAR. Las tasas de retención en el TAR siguen siendo similares a las observadas en los modelos basados en derivaciones médicas.

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