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Achieving UNAIDS 90-90-90 targets for pregnant and postpartum women in sub-Saharan Africa: progress, gaps and research needs

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Abstract

The implementation of the 2013 World Health Organization Option B+ recommendations for HIV treatment during pregnancy has helped drive significant progress in achieving universal treatment for pregnant and postpartum women in sub-Saharan Africa (SSA). Yet, critical research and implementation gaps exist in achieving the UNAIDS 90-90-90 targets. To help guide researchers, programmers and policymakers in prioritising these areas, we undertook a comprehensive review of the progress, gaps and research needs to achieve the 90-90-90 targets for this population in the Option B+ era, including early infant HIV diagnosis (EID) for HIV-exposed infants. Salient areas where progress has been achieved or where gaps remain include: (1) knowledge of HIV status is higher among people with HIV in southern and eastern Africa compared to western and central Africa (81% versus 48%, UNAIDS); (2) access to antiretroviral therapy (ART) for pregnant women has doubled in 22 of 42 SSA countries, but only six have achieved the second 90, and nearly a quarter of pregnant women initiating ART become lost to follow-up; (3) viral suppression data for this population are sparse (estimates range from 30% to 98% peripartum), with only half of women maintaining suppression through 12 months postpartum; and (4) EID rates range from 15% to 62%, with only three of 21 high-burden SSA countries testing >50% HIV-exposed infants within the first 2 months of life. We have identified and outlined promising innovations and research designed to address these gaps and improve the health of pregnant and postpartum women living with HIV and their infants.

Keywords: prevention of mother-to-child transmission, prevention of vertical transmission, HIV, pregnancy, postpartum, sub-Saharan Africa

Introduction

The expansion of HIV care and treatment for pregnant and postpartum women in sub-Saharan Africa (SSA) exemplifies a significant achievement in the global HIV response. In southern and eastern Africa, home to 50% of the HIV population globally, antiretroviral therapy (ART) coverage for pregnant women has increased from 47% in 2010 to 93% in 2017 [1]. A variety of tools and evidence-based strategies have emerged to improve the health of pregnant and postpartum women with HIV, encouraging optimism towards achieving the ambitious targets established by the Joint United Nations Programme on HIV/AIDS (UNAIDS): that 90% of people living with HIV (PLHIV) know their status, 90% of diagnosed people are on ART, and 90% of those on ART are virally suppressed by 2020 [2,3]. Progress in the prevention of mother-to-child transmission (PMTCT) of HIV has also been substantial. With adequate adherence, ART carries the potential to virtually eliminate the risk of vertical HIV transmission for pregnant and breastfeeding women. At the country level, achieving ≥95% population-level ART coverage for pregnant women is a process indicator for national elimination of MTCT (defined as MTCT rates <5% in breastfeeding populations or <2% in non-breastfeeding populations) [4-8].

However, progress across SSA has not been uniform, and as our understanding of the HIV epidemic has deepened, critical gaps

have been identified, which will need to be addressed in order to achieve the 90-90-90 goals for pregnant and postpartum women. Examples of these gaps include: (1) facility-based HIV testing has been broadly implemented for pregnant women in much of southern and eastern Africa, but central and western Africa are lagging behind [9]; (2) from country to country, the proportions of pregnant women accessing ART vary considerably, with many still far from reaching the second 90, even as others have surpassed it [10]; (3) achieving and sustaining viral suppression throughout pregnancy, delivery and the breastfeeding period remains a challenge in multiple countries [11,12], and as a result, there were still an estimated 180,000 new HIV infections in children in 2017 [1]; and (4) for HIV-exposed infants, gaps in early infant diagnosis remain substantial [13]. In this review, we summarise recent progress, remaining knowledge gaps, and identify the future research needed to achieve and eventually surpass the 90-90-90 targets for pregnant and postpartum women in SSA (Table 1).

First 90: knowledge of HIV status

Globally, an estimated 75% of all PLHIV knew their status in 2017, and across many SSA countries, knowledge of HIV status is higher among women of reproductive age (15–49 years) as compared to men [1]. Universal HIV testing for pregnant women initiating facility-based antenatal care (ANC) has been broadly implemented in many regions in southern and eastern Africa, yet central and western Africa, where the healthcare delivery systems are weaker, have been slower to implement this approach [9]. Further, general knowledge of HIV status among PLHIV in western

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Table 1. Research priorities to achieve 90-90-90 for pregnant and postpartum women in sub-Saharan Africa

First 90
<ul style="list-style-type: none"> • Identify approaches to detecting acute HIV infection in pregnancy and postpartum periods • Determine structural- and individual-level barriers to repeat testing in late pregnancy and breastfeeding periods • Evaluate strategies to ensure universal uptake of antenatal services, including HIV testing • Develop innovative testing approaches to identify HIV-positive pregnant/postpartum women in lower HIV-prevalence regions
Second 90
<ul style="list-style-type: none"> • Further understand barriers to ART uptake and retention in care • Assess interventions to improve ART uptake and retention in care • Explore optimal models of integrated HIV and maternal and child health services • Evaluate differentiated models of care for pregnant and postpartum women on ART • Develop strategies to identify and mitigate ART-associated adverse birth outcomes
Third 90
<ul style="list-style-type: none"> • Promote research, country and programme reporting of viral load outcomes during pregnancy and breastfeeding • Evaluate interventions that promote sustained adherence to ART, focused on postpartum period • Determine optimal timing and frequency of viral load monitoring in pregnancy and postpartum • Evaluate biomedical and behavioural approaches designed to achieve rapid viral suppression during pregnancy and breastfeeding
Early infant diagnosis of HIV for HIV-exposed infants
<ul style="list-style-type: none"> • Evaluate integrated approaches to ensure universal uptake of early infant diagnosis • Optimise retention, through the breastfeeding period, of exposed infants • Establish best strategies to incorporate birth testing and point-of-care EID technologies • Develop HIV testing approaches for infants of women with acute infection during breastfeeding

and central Africa is considerably lower than other African regions – at 48%, as compared to 81% in southern and eastern Africa [1]. Stigma and discrimination, test kits stock outs, healthcare worker shortages and user fees all contribute to undermining achievement of the first 90 for pregnant and postpartum women [14]. In addition, as many as 20% of women in SSA are estimated to have no antenatal care, and thus miss antenatal HIV testing entirely [15]. To complicate matters further, pregnancy and the perinatal period are associated with an increased risk of HIV acquisition [16,17]. In a cohort of over 1300 pregnant women in western Kenya, followed through 9 months postpartum, HIV incidence was 2.31 per 100 person-years [18]. Studies from Tanzania and Zambia [19] demonstrated similar results [20]. A critical testing gap also exists for sexually active adolescent girls, particularly in western and central African countries. For example, in Nigeria, 33% of adolescents (ages 10–19 years), as compared to 52% of adult women, reported being tested for HIV during their last pregnancy [21,22].

Several evidence-based strategies exist to improve HIV testing uptake among pregnant women, with fewer strategies specifically focused in the postpartum or breastfeeding periods. Universal, opt-out testing in ANC clinics has been highly successful in eastern and southern Africa. Repeat testing during pregnancy, and at least once during breastfeeding, is cost-effective, although it has

been implemented with varying success [23,24]. Door-to-door testing by lay healthcare workers, and recent approaches integrating immediate ART initiation with community testing, may improve knowledge of HIV status pre-pregnancy, and identify pregnant women who have not enrolled in ANC [25,26]. Testing as part of home-based couples counselling may be particularly beneficial for women who are afraid of knowing their status and disclosing to their partner(s) [26]. Self-testing is an emerging strategy that may be particularly beneficial for sexually active adolescent girls [27–29]. Increased knowledge of personal HIV status among the general population using promising approaches, such as integration of HIV testing within multi-disease health campaigns, is likely to increase the proportion of women who know their HIV status prior to pregnancy and breastfeeding [30,31].

Important research gaps exist that need to be filled in order to improve knowledge of HIV status in pregnant and postpartum women. Identification and assessment of innovative HIV testing strategies that consider the lower HIV prevalence are needed for west and central Africa. Furthermore, approaches to improving uptake of antenatal care in women with low ANC attendance, including community-based peer navigators or thoughtful engagement of traditional birth attendants to promote HIV testing, should be explored. Further work is needed to identify optimal timing and implementation of repeat HIV testing for women, and to better understand structural and individual level barriers to repeat testing [32]. Testing strategies that take into account the unique developmental stage and challenges facing pregnant adolescents need to be identified and evaluated in order to increase testing uptake in this population.

Second 90: uptake of ART

The scale-up of World Health Organization (WHO) recommendations, including Option B (ART for all women through pregnancy and breastfeeding) and Option B+ (lifelong ART for pregnant women), has yielded remarkable progress in ART coverage for pregnant and postpartum women in SSA (Figure 1). ART access for PMTCT more than doubled in 22 of 42 SSA countries with available UNAIDS Global AIDS Monitoring (GAM) data, and six countries (Botswana, Namibia, South Africa, Swaziland, Uganda and Zimbabwe) have surpassed the second 90 target for pregnant women as of 2016 [4,10]. Yet, wide variations in ART coverage exist within the continent, with fewer than 40% of HIV-positive pregnant women accessing ART in Nigeria and Mali compared to over 95% in Botswana, South Africa and Uganda in 2016 [10]. Furthermore, barriers to retention in care and maintenance on ART have surfaced as key obstacles to achieving the second 90 in SSA [33–36]. Since the implementation of Option B+, pooled retention estimates across SSA suggest that one-in-four women become lost to follow-up within 6 months of ART initiation [37], with women initiating ART during pregnancy up to five times more likely to become disengaged compared to women starting ART because of advanced HIV disease [35]. Adverse birth outcomes as a result of *in utero* ART exposure are persistent concerns, as various studies have reported increased risk of preterm birth and low birth weight, which are themselves associated with increased newborn morbidity and mortality in resource-limited settings [5,38,39]. Protease inhibitors, and to a lesser extent nucleoside and non-nucleoside transcriptase inhibitors, are most often associated with these adverse birth outcomes. Of particular concern is a preliminary report of increased neural tube defects in women who conceive on the integrase inhibitor dolutegravir, which is a potent and well-tolerated antiretroviral agent, whose use is rapidly growing in SSA [40,41].

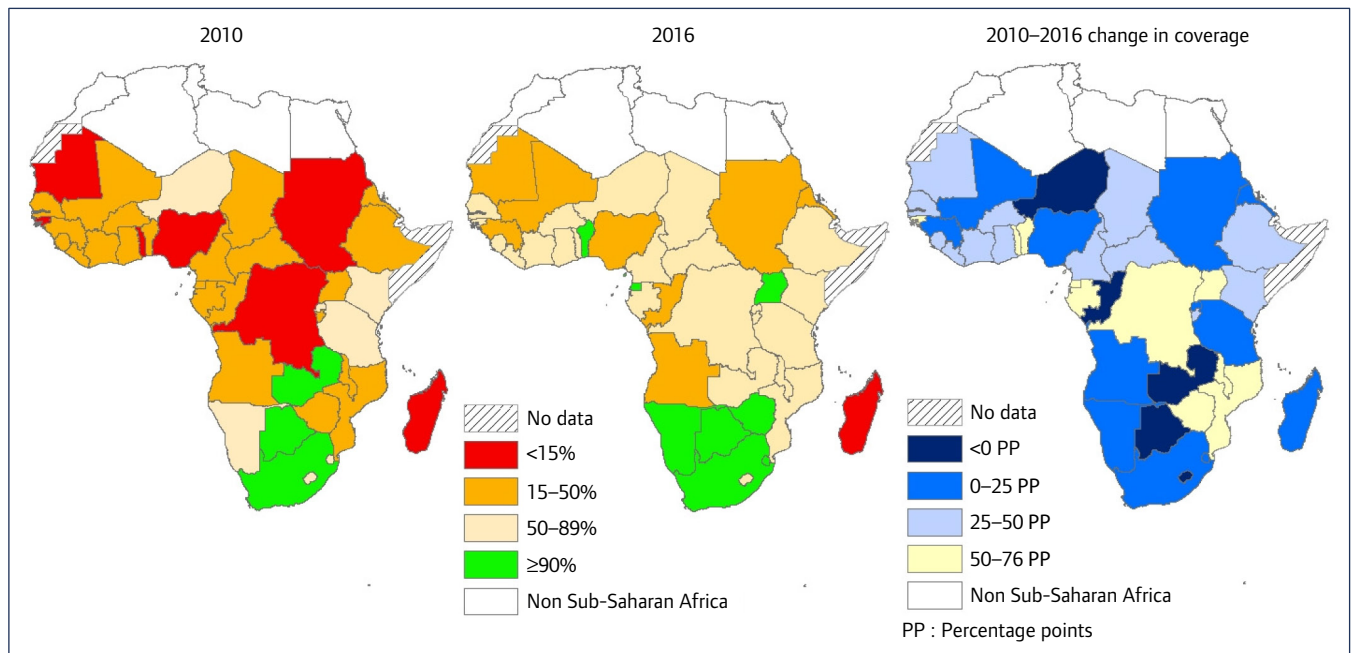


Figure 1. Antiretroviral therapy coverage for pregnant women living with HIV in sub-Saharan Africa, 2010–2016 (excluding single-dose nevirapine). Data from [10]

A variety of evidence-based, scalable interventions have been described that could help reach the second 90 in SSA [42]. These interventions span the social, behavioural and structural aspects of PMTCT care at both the facility and community levels [43]. Improved ART uptake and retention has been demonstrated with expert peer support and ‘mentor mothers’ [44,45], individual or group counselling sessions [45], and community health workers who provide supportive supervision, ART counselling and tracing of women who default from care [46–48]. Male partner involvement has also been shown to improve maternal ART uptake [49–51]. Behavioural interventions by way of text message or phone call appointment reminders (mHealth) have been effective in improving ART uptake and retention across multiple HIV populations, and there is promising evidence of their feasibility and potential efficacy in the PMTCT population as well. Economic incentives, such as conditional cash transfer [52] and disclosure support to partners [53] have been less well studied, but may provide additional retention benefits. Structurally, the integration of HIV services into maternal and child health and postnatal services has played an important role in expanding capacity for ART coverage, and may improve retention in care compared to non-integrated services [54,55]. Combination interventions are also increasingly being examined to maximise gains in retention and maintenance on ART [42,56,57]. Finally, although many SSA countries have yet to implement national surveillance for ART-related adverse birth outcomes, researchers in Botswana, through the Botswana-Harvard partnership (Tsepamo study), have established a unique surveillance programme that has contributed key data to inform our understanding about the safety of ART for the mother and fetus [40,41].

Despite important progress, knowledge gaps persist concerning the optimal implementation strategies to achieve the second 90. Overall, the evidence for many of the aforementioned interventions is weak and heterogeneous, with limited duration of effect. Further research is needed to: (1) identify the barriers to care; (2) study the impact of interventions on long-term retention; (3) determine successful integration and differentiated care models for PMTCT; and (4) evaluate strategies to optimise ART uptake while maximising safety. Failure to engage in antenatal and HIV

care threatens not only HIV-exposed infants, but the health of women with HIV and their partners.

Identifying barriers to care is critical, including their relative significance, and the optimal social and behavioural interventions to address them, particularly in terms of their cost-effectiveness and scalability for care programmes. Many studies have looked at the impact of interventions to improve adherence and retention for the period up to 12 months post-delivery; however, breastfeeding and PMTCT follow-up can last 18 months or longer in many cultures. Studying the impact of interventions through the conclusion of PMTCT follow-up, and through the transition back to an HIV clinic for postpartum women, is vital to understanding their durability and true effect sizes.

On a structural level, integrated service delivery models that maximise efficiency and efficacy for stable PMTCT clients, including models of differentiated and decentralised ART delivery, and patients’ preferences for such models, need to be rigorously evaluated [58]. High-quality, large, population-based studies to better understand the factors that drive regional variations in ART coverage for pregnant and postpartum women in SSA will also help achieve the second 90 goals for them. Finally, questions remain concerning the timing of ART initiation, and the effects of established and novel ART regimens (e.g. dolutegravir) on adverse birth outcomes (e.g. stillbirth, preterm birth, growth restriction, congenital anomalies) and infant development [41,59–61].

Third 90: viral suppression

Achieving and maintaining viral suppression is urgent for pregnant and postpartum women in order to minimise vertical HIV transmission and maximise women’s health outcomes [62]. While routine viral load monitoring among PLHIV on ART is now recommended by WHO, scale-up has been slow. In a study focused on seven of the SSA countries, only one was performing at least one viral load on more than 85% of patients on ART (South Africa [91%]); two countries (Kenya [40%] and Namibia [23%]) tested fewer than 50% of patients on ART, and four countries (Côte d’Ivoire [11%], Malawi [19%], Tanzania [9%], and Uganda [22%]) tested

fewer than 25% [63]. Further, recognition of pregnant and postpartum women as a priority population for monitoring and rapid intervention in the setting of virological failure is lacking [63–65]. As a result, literature on viral suppression among pregnant and breastfeeding women in SSA is sparse and frequently comes from research studies rather than routine care programmes. Additionally, several of these studies were conducted in settings and during time periods when universal ART was not the standard of care, and thus have a mixed population of women who are on ART as well as those on PMTCT prophylaxis [66].

Available data show viral suppression rates at delivery or immediately postpartum have ranged from 30% to 98% in different SSA settings, and are dependent on the viral load threshold used (Table 2). Keeping women engaged in care and optimally adherent to ART following delivery is a well-known challenge, and undermines sustained viral suppression [35,48]. In Malawi, although 70% of women starting ART during pregnancy and breastfeeding had adequate adherence (defined as having ART drugs available $\geq 90\%$ of days between clinic visits), only one-third of them maintained adequate adherence over 2 years of treatment [67]. Similarly, among women who became pregnant after initiating ART in South Africa, the risk of non-adherence was nearly 50% higher during the postpartum period compared to the non-pregnant period [68,69]. Further, even among those who are retained in care, optimal viral control ($>90\%$ with VL <50 copies/mL) in the postpartum period is rarely achieved. In Nigeria, only 58% of women attained suppression (<20 copies/mL) at 6 months postpartum [70]. While in a follow-up study of 523 previously virally suppressed (<50 copies/mL) women in Cape Town, only 70% were able to maintain viral suppression through 12 months postpartum [11]. The most promising and longest follow-up comes from the PROMOTE trial in Uganda, in which approximately 90% of women had VL <400 copies/mL at 24 months postpartum [71]; and 5 years later, among a random sample of 200 participants, 90% had maintained viral suppression [72].

Evidenced-based approaches to address the main drivers of virological failure are being elucidated. While in many settings, data are lacking or not well utilised to address gaps in the third 90, South Africa's rapid and successful scale-up of PMTCT has been attributed to the use of data-driven continuous quality improvement interventions that identify problems as they emerge, and empowers front-line staff to create local solutions [77,78]. This strategy is currently being fully evaluated in a cluster randomised trial focused on women initiating ART in pregnancy or during breastfeeding in the Democratic Republic of Congo [57]. A large number of studies have identified that non-adherence in pregnancy and the postpartum period is multifactorial, and may be driven by individual-level and biomedical issues, such as ART toxicity, stigma, mental health, ART toxicity and comorbidities, and structural issues related to healthcare worker attitudes and the availability of supportive services [11,66,72–74,79–84]. Thus, combination strategies that address these challenges are needed. Several studies are currently evaluating behavioural, peer navigator and mHealth interventions that may prove successful in attaining and maintaining viral suppression for pregnant and postpartum women [85,86].

In order to reach the third 90 for pregnant and postpartum women, the lack of data highlighted above, especially data from routine PMTCT implementation at programme and country level, will need to be addressed. Additionally, there is need for evidence-based interventions that improve engagement in care and adherence on ART among pregnant and breastfeeding women, and target previously identified modifiable predictors of viral suppression in this population. In order to achieve the third 90 for

pregnant and postpartum women, a research agenda targeted on addressing sustained adherence is vital. Additional research should address the optimal timing and frequency of VL monitoring in pregnant and postpartum women and biomedical and behavioural interventions that rapidly achieve suppression in women with viremia.

Early infant diagnosis for HIV-exposed infants

Over 80% of newly infected children acquire their HIV infection through MTCT, yet fewer than 50% of infants exposed to HIV are tested at 6 weeks of age, and up to 45% are lost after initial testing [14,48]. EID is the crucial first step in addressing the alarmingly high mortality rate for infants infected with HIV, and is intricately linked with 90-90-90 goals for pregnant and postpartum women [87]. Some countries in SSA have made significant progress scaling-up EID testing; in a report on six SSA countries (Cote d'Ivoire, Democratic Republic of Congo, Malawi, South Africa, Uganda and Zambia) it was noted that the total number of EID tests performed on HIV-exposed infants significantly increased between 2011 and 2015, but testing before 6 weeks of age was poor, ranging between 15% and 62% [88]. In 2016, among the 21 UNAIDS-designated high-burden countries (all of which are in SSA) (90), only three – South Africa, Swaziland, and Zimbabwe – managed to test over 50% of exposed infants within the first 2 months of life [14,89]. Even when infants are tested, turn-around time for test results is so exceptionally long that caregivers may never receive the results [90].

Multiple strategies are gaining evidence of effectiveness in improving the first 90 for exposed infants in SSA. South Africa is the first high-burden country to introduce routine birth testing for exposed infants, and has achieved greater than 90% coverage. Complexities of neonatal HIV treatment, and high rates of early losses to follow-up after birth testing, remain concerns for the introduction of birth testing on a wide scale [91,92]. Point-of-care diagnostics may also be a promising new strategy that avoids the challenges associated with sample transport to centralised laboratories, and facilitates early intervention for positive results [93,94]. mHealth innovations, such as returning test results via short text message (SMS), electronic tracking systems and national web-based result dashboards, such as those being used in Kenya and South Africa, may support improved uptake as well as efficient return of results to providers and caregivers [95–97]. Integration of maternal and child health services, and psychosocial support through peer or community interventions, supports EID and retention of both mothers and exposed infants [49,54,98–101].

Further research into testing strategies that maximise uptake and facilitate early ART for infected infants are needed. How and where to integrate accurate point-of-care technologies into national EID algorithms, including as testing at birth, need to be determined. Strategies for integrating surveillance for acute HIV infection in pregnant and breastfeeding women with EID for infants should be explored. Further evidence is needed for cost-effective psychosocial support models that encourage HIV testing among exposed infants.

Conclusion

Despite considerable expansion of quality PMTCT services, and widespread uptake of Option B+, most countries in SSA have not achieved UNAIDS 90-90-90 targets for pregnant and postpartum women. A targeted research agenda as outlined in this paper is an important next step in reaching these critical goals, in order to achieve the elimination of vertical HIV transmission and ensure the health and well-being of women and their families.

Table 2. Summary of studies on the prevalence of viral suppression in sub-Saharan Africa

Author	Enrolment period	Region	Design	ART eligibility and naivety status	Timing of enrolment	Analytical sample	Viral load threshold (copies/mL)	Timing of VL sampling	Prevalence (%)
Chagomerana <i>et al.</i> [73]	Jun 2015–Nov 2016	Lilongwe, Malawi	Prospective cohort	ART-naïve and experienced	First ANC of current pregnancy	252	<1000	Delivery	84
							<40	Delivery	69
Chetty <i>et al.</i> [12]	2010–2015	Rural KwaZulu-Natal, South Africa	Prospective cohort	ART-experienced (at least 6 months)	Pregnancy, during first ANC visit	1425	<1000	Pre-pregnancy	89
								Pregnancy	85
								6 months postpartum	84
								12 months postpartum	82
							<50	25 months postpartum	83
								Pre-pregnancy	82
								Pregnancy	77
								6 months postpartum	77
12 months postpartum	76								
25 months postpartum	76								
Cohan <i>et al.</i> [71]	Dec 2009–Mar 2013	District Tororo, Uganda	Randomized control trial (test efficacy of efavirenz vs lopinavir/ritonavir)	ART naïve-eligible	Pregnant, 12–28 weeks	389	<400	Delivery (efavirenz arm)	98
								Delivery (lopinavir/ritonavir arm)	86
								48 weeks postpartum (efavirenz arm)	91
								48 weeks postpartum (lopinavir/ritonavir arm)	88
Gill <i>et al.</i> [74]	Apr 2013–Jan 2014	Kigali, Rwanda	Prospective cohort	ART-naïve and experienced	Third trimester of pregnancy and up to 2 weeks post-partum	608	<20	≤4 months under ART	30
								>4 months under ART	66
								>12 months under ART	66
								>12 months under ART	90
Hosseinipour <i>et al.</i> [75]	Jan 2003–Mar 2017	Central and southern Malawi	Randomized control trial	ART naïve-eligible	Pregnancy or post-partum	1269	<1000	6 months post enrollment	84
Koss <i>et al.</i> [72]	Mar 2015–Sept 2015	District Tororo, Uganda	Cross-sectional	ART naïve-eligible	Pregnancy, 12–28 weeks	150	<400	Postpartum	90
Myer <i>et al.</i> [76]	Apr 2013–May 2014	Cape Town, South Africa	Retrospective cohort	ART naïve-eligible	First ANC of current pregnancy	620	≤1000	Delivery	91
							≤50	Delivery	73
Myer <i>et al.</i> [11]	Apr 2013–May 2014	Cape Town, South Africa	Prospective cohort	Women who initiated ART during pregnancy and achieved initial viral suppression during follow-up	First ANC of current pregnancy	523	sustained viral load <50 during follow-up	Across follow-up (median 322 days) during the postpartum period: 7 days, 6 weeks, 3 months, 6 months, 9 months, and 12 months	70
Sam-Agudu <i>et al.</i> [45]	Apr 2014–Sept 2015	Federal Capital Territory and Nasarawa states, North-central Nigeria	Prospective cohort	ART-naïve and experienced	Pregnancy, mixed gestational ages	497	<20	Postpartum	58

ANC: antenatal clinic; cp: copies; VL: viral load.

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