A systematic review of the effects of interrupted antiretroviral interventions for prevention of mother-to-child transmission of HIV on maternal disease progression and survival

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Overview

- Background
- Objective
- Methods
- Results
- Discussion

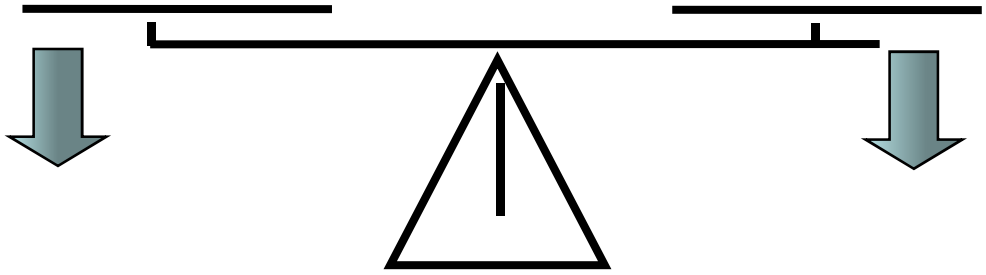
Background

- Antiretroviral (ARV) interventions are effective at prevention of vertical transmission of HIV during pregnancy, delivery and breastfeeding.

- For HIV-positive mothers not yet requiring lifelong antiretroviral therapy (ART), the long term effects of interrupting triple ARVs on maternal health and survival remain unknown.

Interrupted versus continued ART for PMTCT

Benefits	Risks
↓ MTCT risk?	Safety
Programmatic issues	Disease progression
Maternal health	Resistance
	Acceptability
	Cost effectiveness



Objectives

To assess the literature of maternal disease progression (clinical, immunological, virological) and maternal mortality in HIV-positive pregnant women who received interrupted triple ARVs for prevention of mother-to-child transmission (PMTCT).

Methods

- **Assessed randomised controlled trials (RCTs) and cohort studies (Cs) of**
  - HIV-positive pregnant women who
  - received triple ARVs for PMTCT interrupted after pregnancy
  - or breastfeeding,
  - compared to women on cART,
  - for the effect on maternal mortality and disease progression
    - clinical: new WHO stage 3 or 4 events,
    - immunological: CD4<350,
    - virological: VL increase >0.5log
  - As there were limited RCTs addressing this question, observational cohorts that provided data on maternal mortality and disease progression by the three drug intervention groups were included.

Methods

- **Types of participants**

  HIV-positive pregnant women who were ART naïve in the current pregnancy, who were followed up for 6, 12, 18 or 24 months after delivery

- **Types of interventions**
  - Short course ARV (sd-NVP; ZDV dual therapy);
  - Triple ARVs (triple ARVs for PMTCT interrupted after delivery or breastfeeding); and
  - ARTs (lifelong HAART or continuous ART).

Methods

- **Types of outcome measures**
  - Primary outcomes at pre-intervention, birth, 6, 12, 18 or 24 months postpartum:
  - All cause maternal mortality;
  - Maternal CD4 count;
  - Maternal Viral Load; and
  - Maternal WHO clinical staging.

Methods

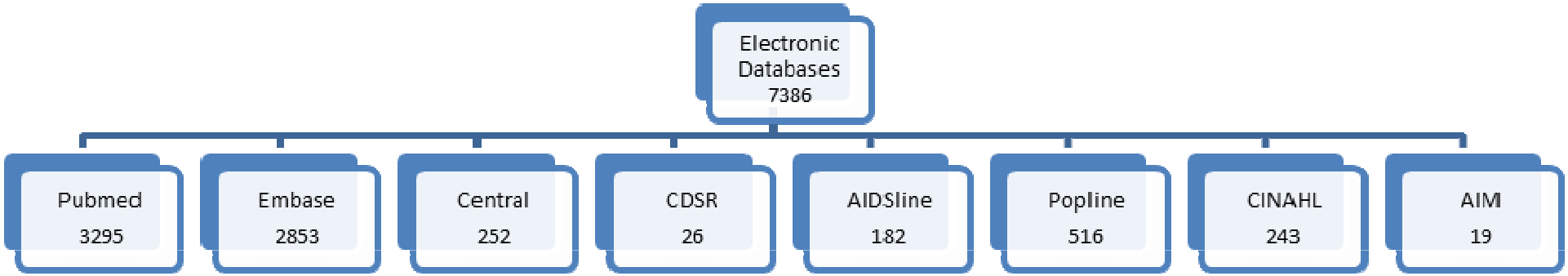
- **Search Strategy**
  - In September 2011, searches were conducted in 8 electronic databases. Abstracts from 5 conferences over the past 3 years were searched.
  - Hand searches were performed on reference lists of all pertinent reviews and experts were contacted to locate additional publications.

Methods

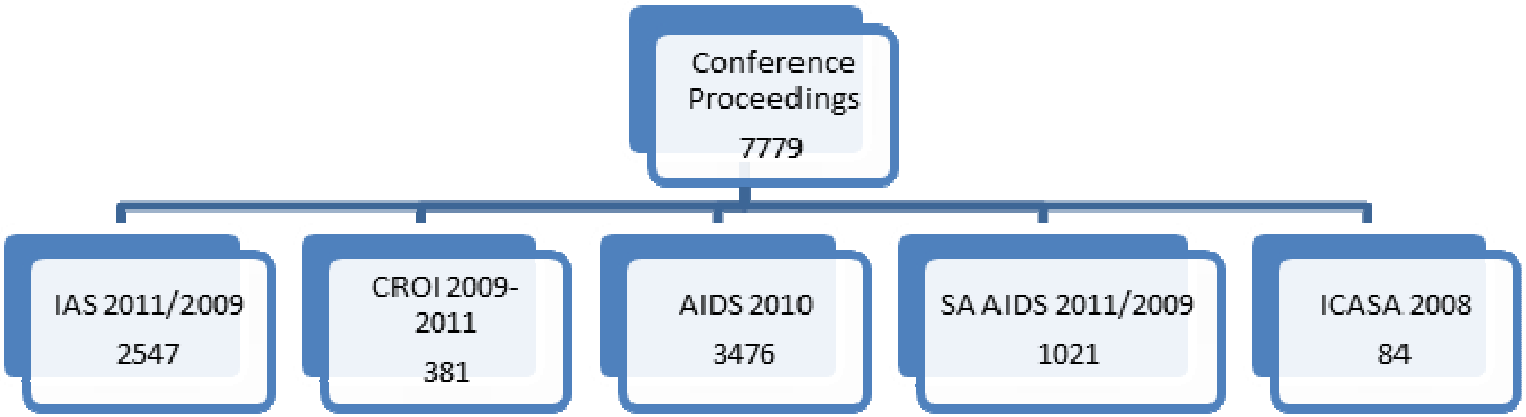
- **Data collection and analysis**
  - Search strategy following the Cochrane Reviewers' Handbook methodology
  - Titles of all appropriate abstracts and titles collected from electronic and hand searches entered into the Endnote
  - Irrelevant and duplicate texts and articles discarded
  - Standardised data extraction form used
  - Summary tables and risk of bias compiled
  - Heterogeneity assessment

Results

Electronic databases searched

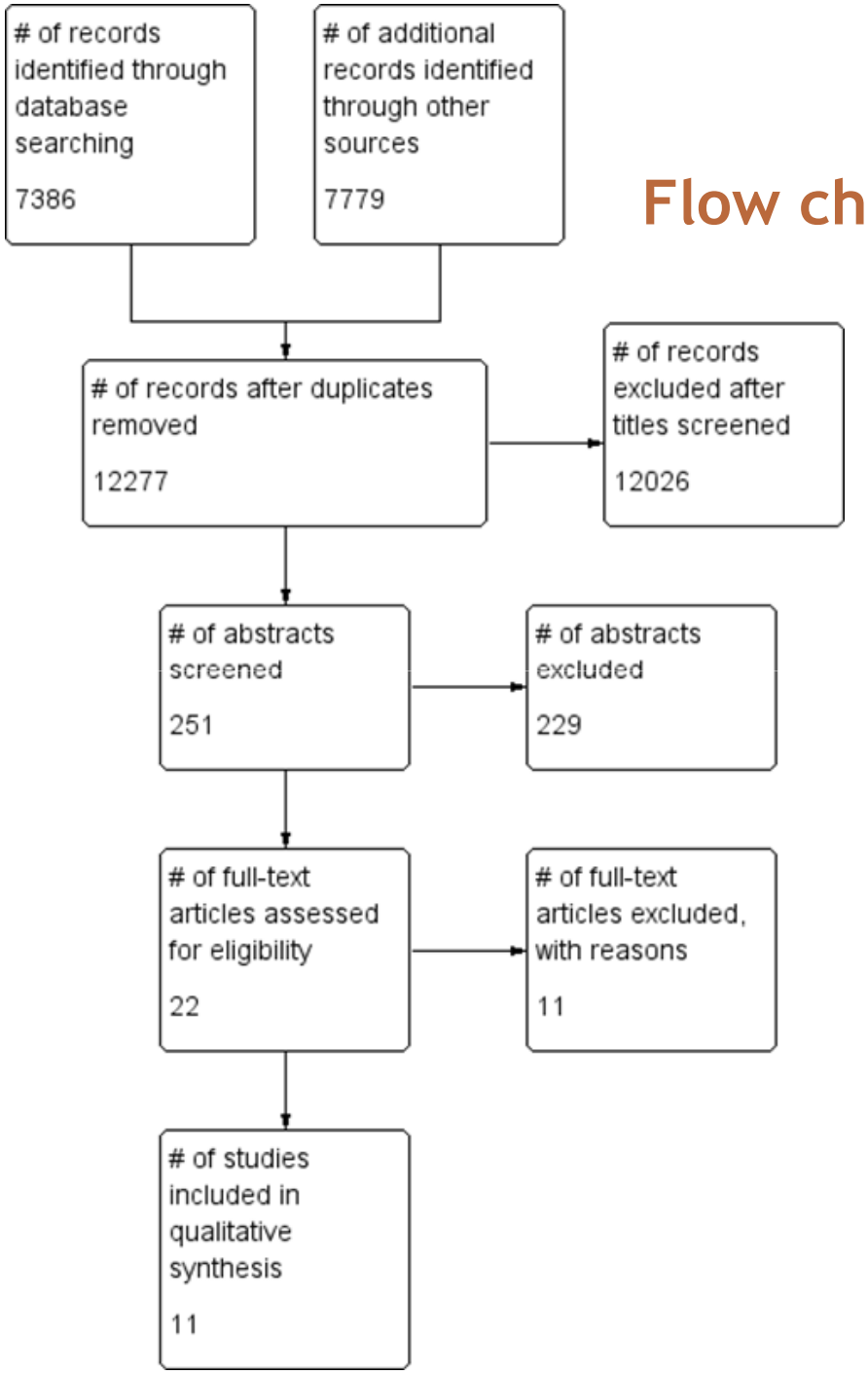


Conference proceedings searched



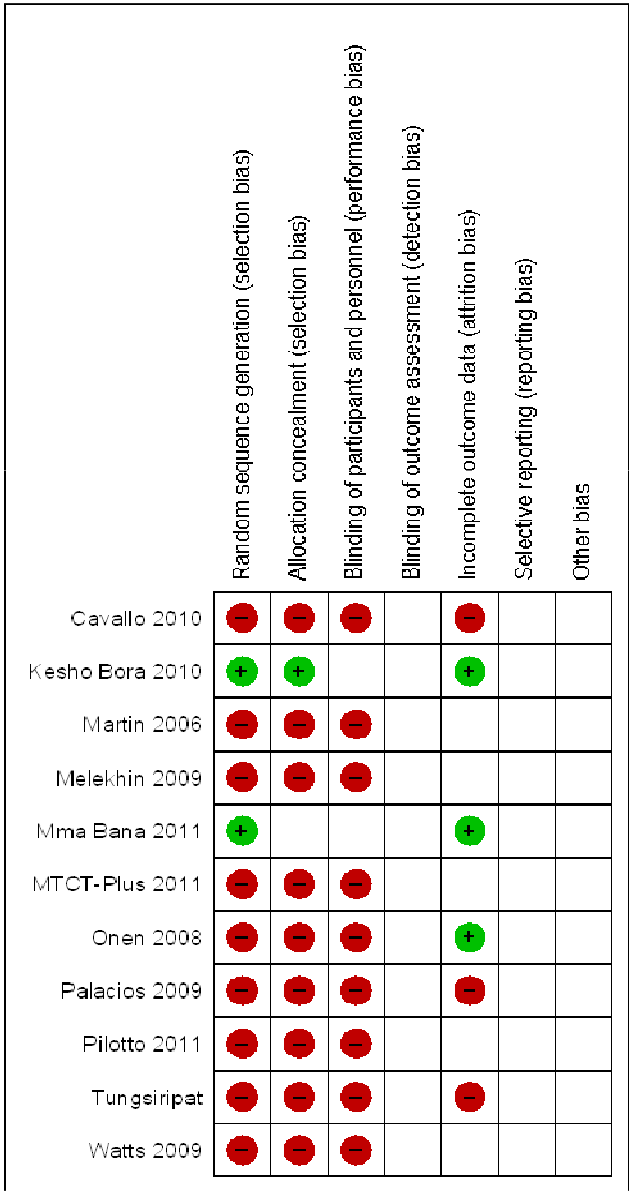
Results

Flow chart for the screening process



Results

Risk of bias assessment



Results

- Meta-analysis could not be conducted due to inter-trial heterogeneity in terms of drug interventions and outcome measures.

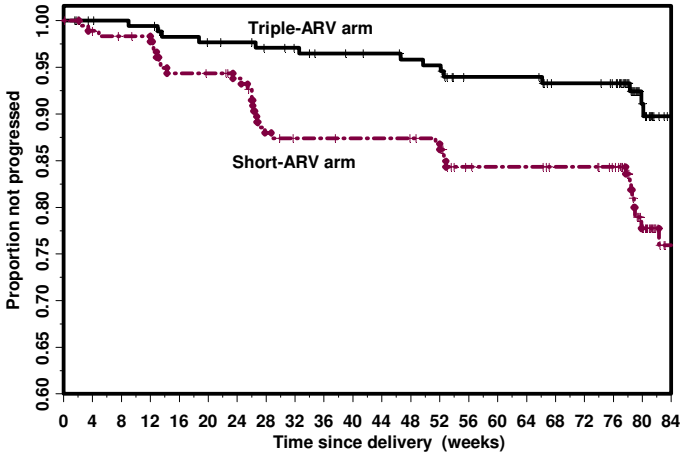
- Five studies (one RCTs and four Cs) were suggestive of increased maternal disease progression and mortality in interrupted ARV group versus cART; the remaining six studies showed no effect.

Results

Study	Study design / Setting	Intervention	Quality	Mortality	Immunologic	Virological	Clinical
Kesho Bora	RCT	AZT, 3TC, LPV/r until BF completed versus ZDV, sd-NVP	Low risk	Short ARV/delivery, % (n) 18 months: 13.7% (51) Triple ARV/delivery 18 months: 8.3% (30) Triple ARV / end ARV prophylaxis 18 months: 13.1% (32)		Cumulative rates of disease progression 18 months after delivery were lower in the triple ARV versus short arm (log rank P = 0.004)	
Mma Bana	RCT and cohort	AZT,ABC, 3TC vs AZT, 3TC, LPV/r or AZT, 3TC, NVP	Moderate risk	Maternal deaths, n (%) 24 months: Overall 14 (1.9%); Arm A 6 (2.1%); Arm B 3 (1.1%); Arm C 5 (2.9%)		Mean change in CD4 $^{+}$ (cells/mm^3) 24 months: Overall +134; Arm A +68; Arm B +98; Arm C +283	

Rates of Progression to Stage 3 or CD4<350
Women with CD4>=350 at entry

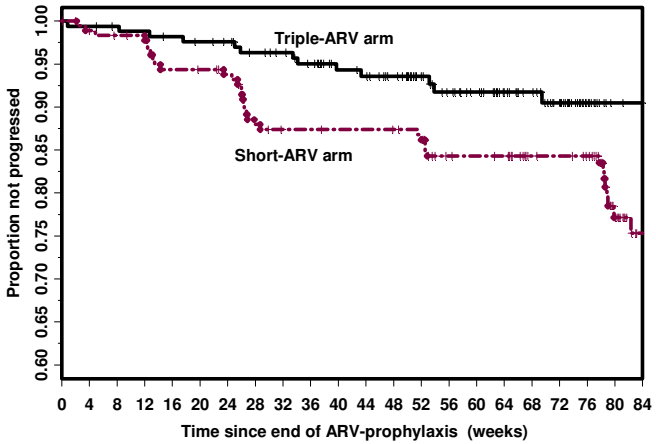
Rate of progression from delivery



	6 months	12 months	18 months
Short-ARV	(182) 12.0%	(151) 15.7%	**(129) 24.1%**
Triple-ARV	(179) 2.9%	(162) 6.1%	**(138) 10.4%**

P=0.002

Rate of progression from stopping ARV-prophylaxis



	6 months	12 months	18 months
Short-ARV	(182) 12.0%	(151) 15.7%	**(129) 24.1%**
Triple-ARV	(168) 3.7%	(152) 8.2%	**(98) 9.5%**

P=0.013

Kesho Bora Study group

Study	Study design / Setting	Intervention	Quality Assessment	Mortality	Immunological	Virological	Clinical
Tungsiripat	Retrospective cohort/ Washington, US	ARV discontinued at delivery	High risk		Median $CD4^+$ count postpartum (643 cells/µl) did not differ significantly from baseline $CD4^+$ count (550 cells/µl)	Median HIV-1 RNA levels postpartum (3.65 $\log_{10}$ copies/ml) did not differ significantly from baseline HIV-1 RNA level (3.63 $\log_{10}$ copies/ml)	
MTCT-Plus	Prospective cohort/ 8 African countries and Thailand	Sd-NVP or AZT/3TC or AZT,3TC, NVP or Nelfinivir	Moderate Risk	CD<350 by 24 months Triple ARV: 36.3%; sc-ARV: 21.5%; sd-NVP: 27.8%; No prophylaxis: 31.7% (p=0.017)	Women on Triple ARV more likely to require ART by 24 months than other groups HR 3.37 (95%CI 1.96 to 5.79, p<0.001)		
Pilotto	Prospective cohort/ Rio de Janeiro, Brazil	2 NRTI + PI or NNRTI interrupted at delivery	High risk	10 required ART during followup due to HIV disease progression CD4 higher than baseline at 12 months post partum (p=0.016)	VL no different than baseline at 12 months post partum	20 developed WHO stage 2/3 events, 1 WHO Stage 4 event	
Cavallo	Prospective cohort / urban Brazil	Prophylactic or therapeutic triple ARV or AZT	High risk		Viral rebound at 6 months in 84.7%(n=50) of prophylaxis arm and 15.3%(n=9) of treatment arm p <0.001		

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Watts	**Prospective cohort / multicentre U/S**	Sc-ZDV or ARVs, or continued ART	Moderate risk	Rate of change of CD4 and VL post delivery not significantly different in interrupted vs continued. CDC class B events increased in interrupted vs continued arm HR 2.09 (95%CI 0.79-5.58, p=0.14)			
Palacios	**Prospective cohort/ Sao Paulo, Brazil**	Interrupted triple ARV, NRTI+NNRTI or PI	High risk	nil	Median time to CD4 less than 300 = 198.1 weeks (95% CI 147.4-248.9)		nil
Onen	**Retrospective cohort/Washington, US**	Discontinuation of ART by 3 months postpartum or continued ART	High risk	2 deaths in the interrupted group, 0 in the continued group			2 OIs in continued group and 10 OIs in the interrupted group (p>0.05)
Martin	**Prospective cohort/ London**	Sc-ZDV or ART or triple ARV	Moderate risk	Sc-AZT = 0 ART = 1 Triple ARV = 0	Median CD4 lowest in the Triple ARV group 397(55-940)	Median VL highest in the Triple ARV group 3.5(1.7-5.9)	Sc-AZT = 3 events ART=4 events Triple ARV= 1
Melekhin	**Prospective cohort/ Nashville, US**	Discontinued ART < 90 days post pregnancy event or continued ART	High risk	Risk of AIDS defining event did not differ HR 0.58 (95%CI 0.14-2.33; p=0.44)		Risk of non-AIDS defining event lower in continued ART group HR 0.35 (95% CI 0.11-1.07; p=0.07)	

Discussion

- These findings were suggestive of increased maternal mortality and disease progression in women who received interrupted triple ARVs compared to women on cART. More research is required to confirm this trend.
- Inclusion of Cs and inter-study heterogeneity increased bias in this study.
- Though inconclusive, these findings support the revision of WHO PMTCT guidelines to Option B+ with cART for life from pregnancy.
- Countries must consider their local context to decide on best option for implementation

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Programmatic issues	**Disease progression ?**
Maternal health ?	Resistance
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