



重庆市公共卫生医疗救治中心
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Optimal Timing of Antiretroviral Therapy for HIV-infected Patients with Cryptococcal Meningitis: A Systematic Review and Meta-analysis

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Background:

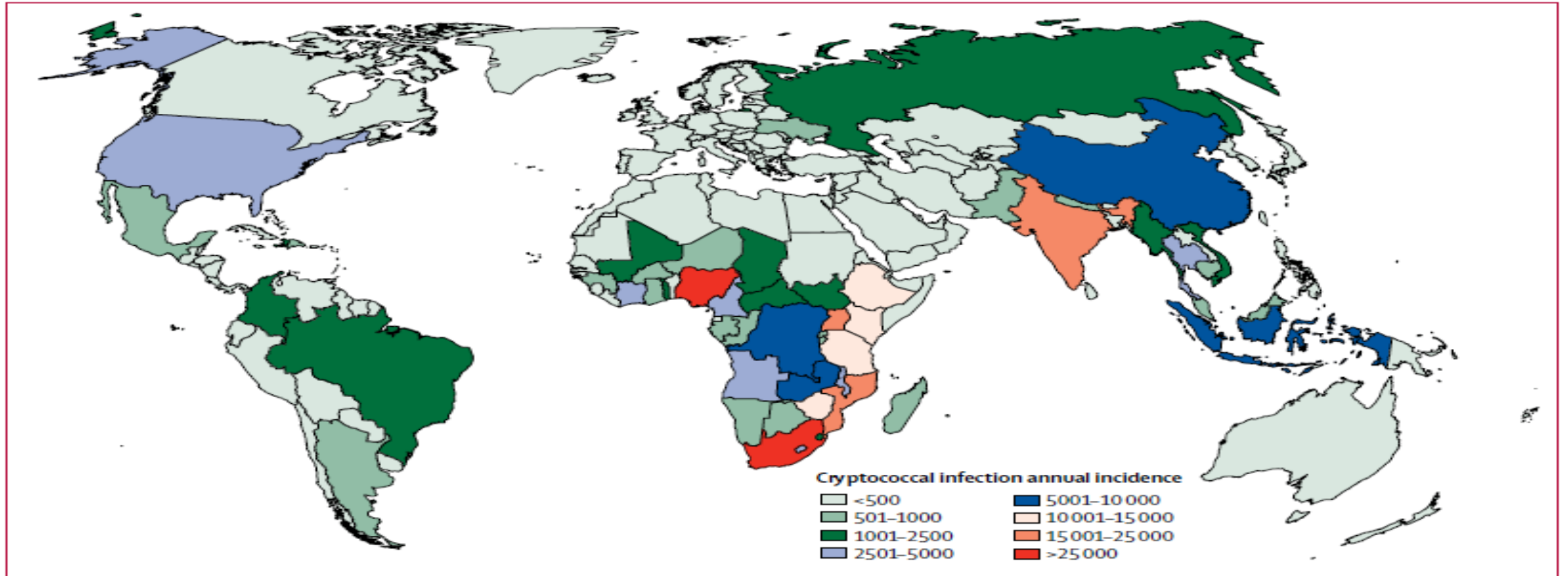


Figure 2: Annual incidence of cryptococcal infection by country

The annual number of people positive with cryptococcal antigenaemia estimated at 278 000 (95% CI 195 500–340 600) globally in 2014. We estimated 223 100 annual incident cases of cryptococcal meningitis in 2014..



- 1. Register: <http://www.cdr.York.ac.uk/prospero> (CRD42018086669)**
- 2. Electronic Database: Pubmed, Embase, Clinical Trials. gov and Cochrane Library databases**
- 3. Key Word: “HIV-infected patients”, “Cryptococcal Meningitis ”**
- 4. Period range: January 1980 to February 2018**
- 5. Research Type: Randomized controlled trials**



Results:

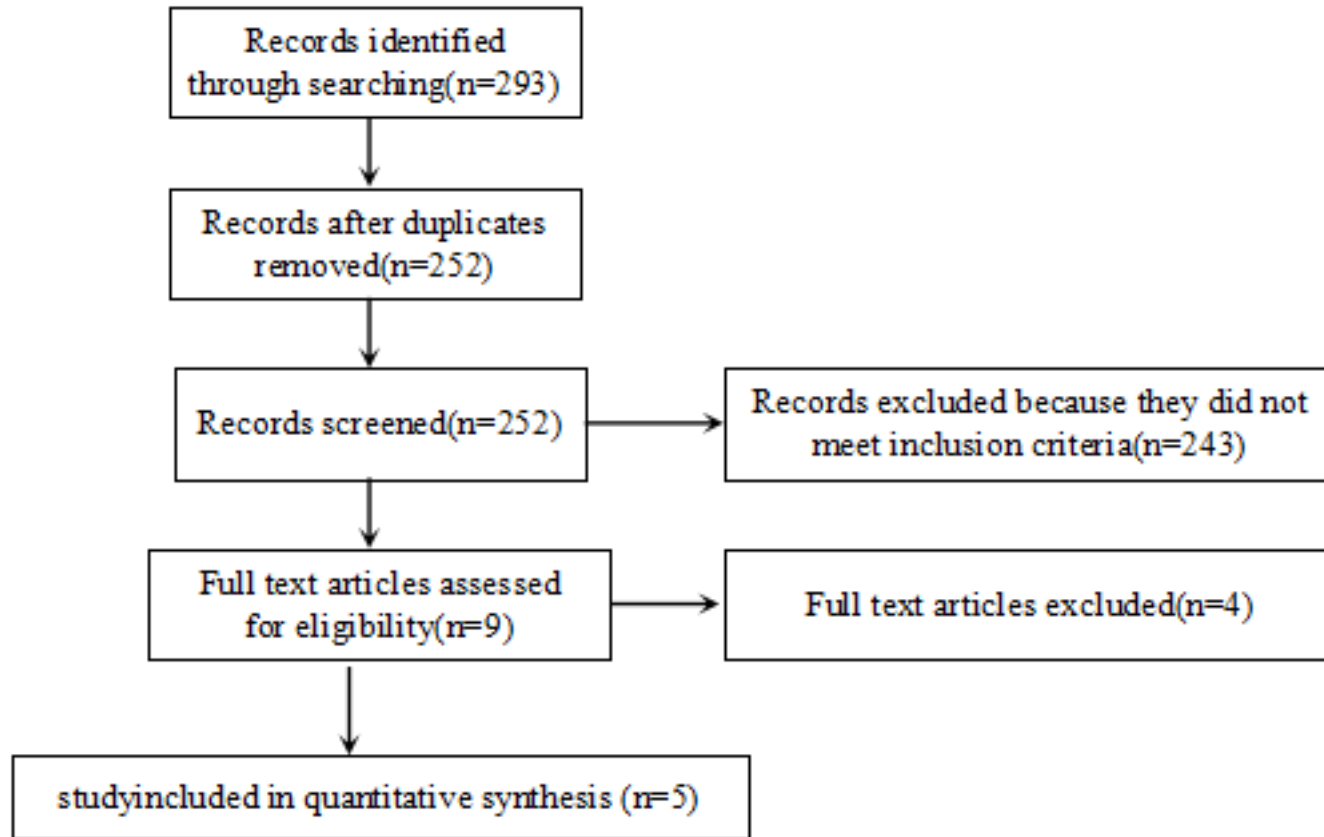


Figure 1 Flow diagram of study selection

Included:

- (1) Patients were HIV-positive;
- (2) Diagnosis of CM was confirmed by positive results of India ink identification of cryptococcus neoformans in the cerebrospinal fluid (CSF) and/or a CSF cryptococcal polysaccharide antigen (CRAG) test;
- (3) Early ART initiation and delayed ART initiation were reported;
- (4) Outcomes of all-cause mortality and development of CM-IRIS were reported;



Table 1. Characteristics of the included trials.

Author	Year	Location	Age (median)	Number		CD4 (median, cell/uL)	HIV-RNA (log10)	Early ART	Delayed ART	ART Regimen	Antifungal Regimen
				EG	DG						
Zolopa/ Grant	2009/ 2010	America	38	13	22	29	5.07	2days-2 weeks	6weeks-12 weeks	LPV/r, FTC, TDF, d4T	NA
Bisson	2013	Botswana	35	13	14	29	5.6	7days	4weeks	TDF, FTC, EFV OR TDF, FTC, NVP	Amphotericin /Voriconazole
Makadzange	2010	Parirenyat wa	36.6	28	26	27	5.09	3days	10weeks	d4T, 3TC, NVP	Fluconazol
Boulware	2014	South Africa	35	88	89	28	5.5	2days	4weeks	AZT/d4T, 3TC, EFV	Amphotericin /Voriconazole

EG=Early Group; DG=Delayed Group; LPV/r=Ritonavir-boosted lopinavir; FTC= Emtricitabine; TDF=Tenofovir; d4T=Stavudine; EFV=Efavirenz; NVP=Nevirapine; 3TC=Lamivudine; AZT=Zidovudine.



	Zolopa/Grant 2009/2010	Makadzange2010	Boulware2014	Bisson2013	
	+	-	+	+	Random sequence generation (selection bias)
	+	+	+	+	Allocation concealment (selection bias)
	-	-	+	-	Blinding of participants and personnel (performance bias)
	+	?	+	?	Blinding of outcome assessment (detection bias)
	+	?	+	+	Incomplete outcome data (attrition bias)
	+	+	+	+	Selective reporting (reporting bias)
	+	-	+	+	Other bias

Figure 2. The graphical representation of the risk bias in all included trials.

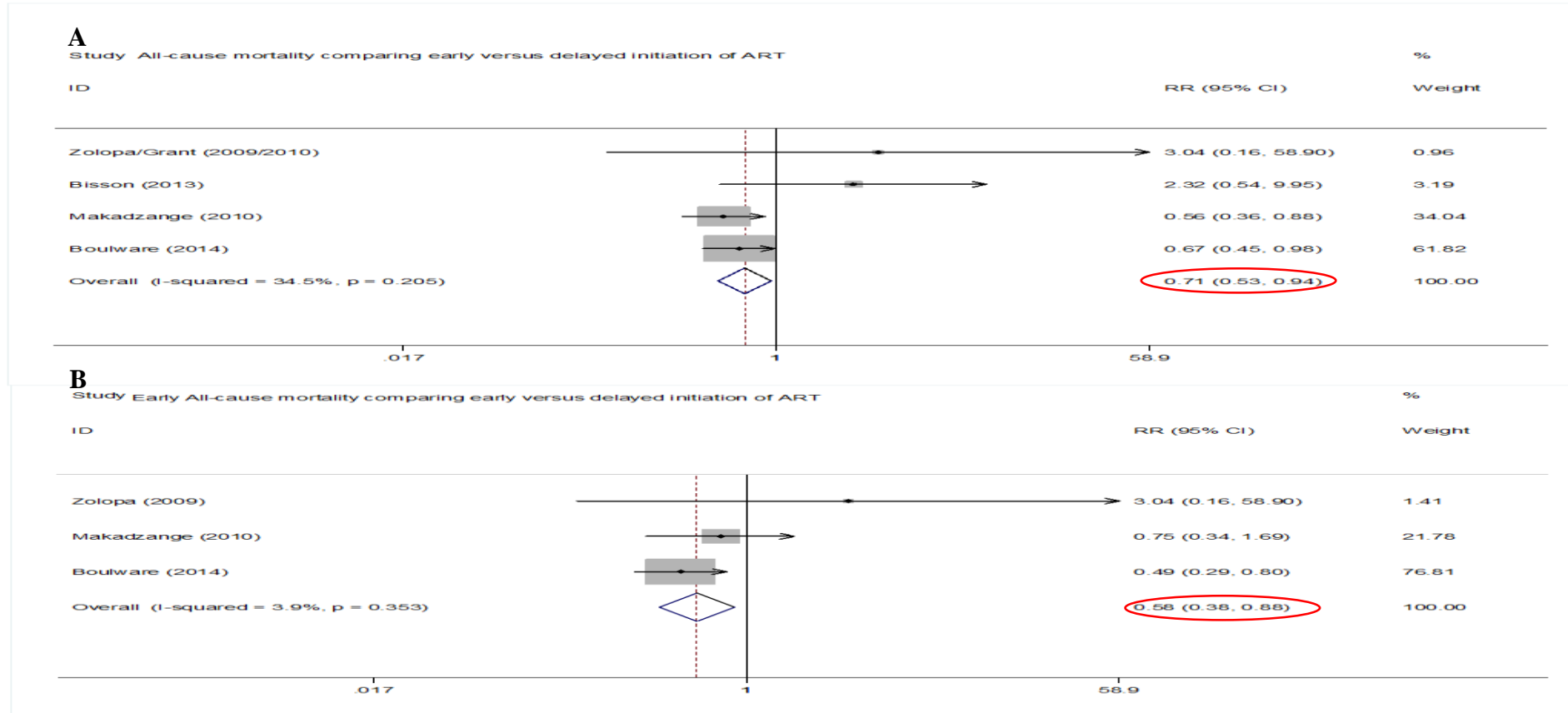


Figure 3. All-cause mortality comparing delayed versus early initiation of ART, stratified by the time of follow up.

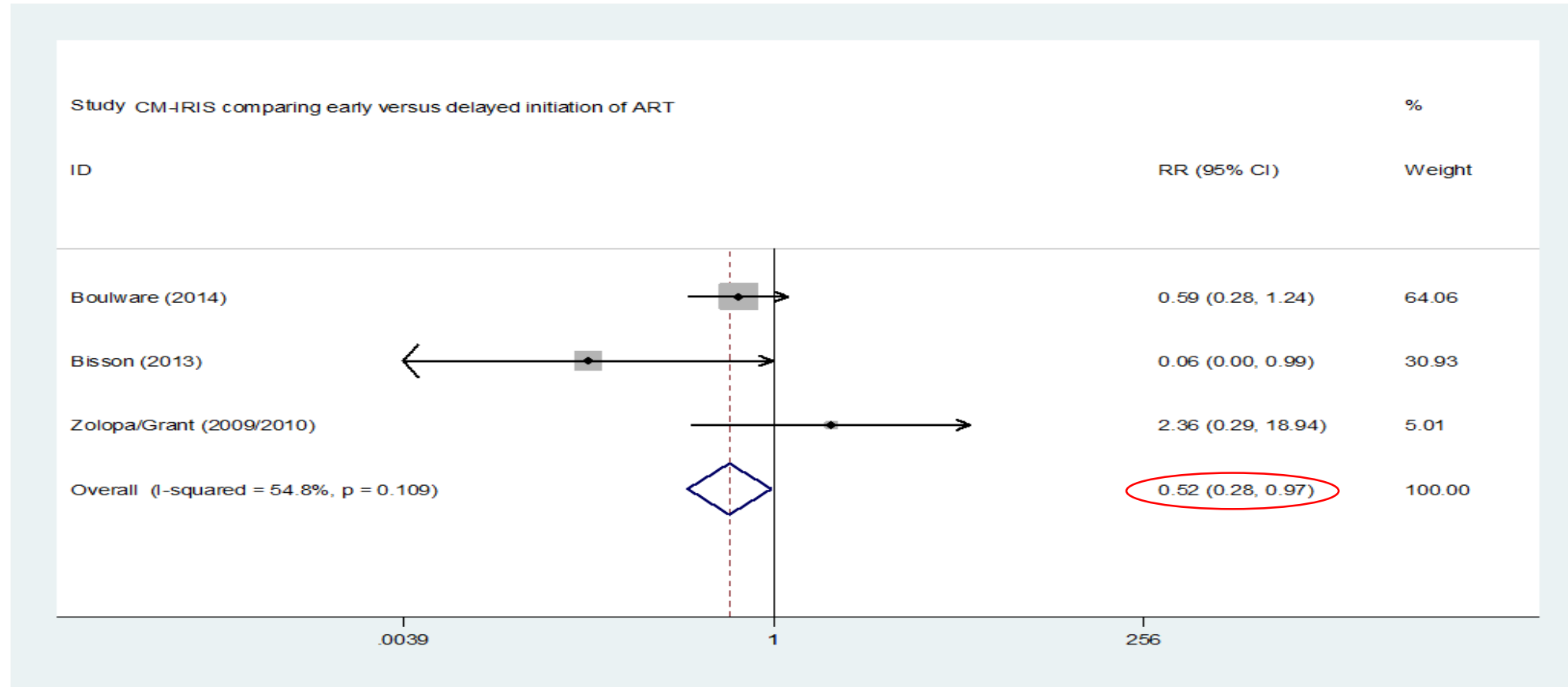
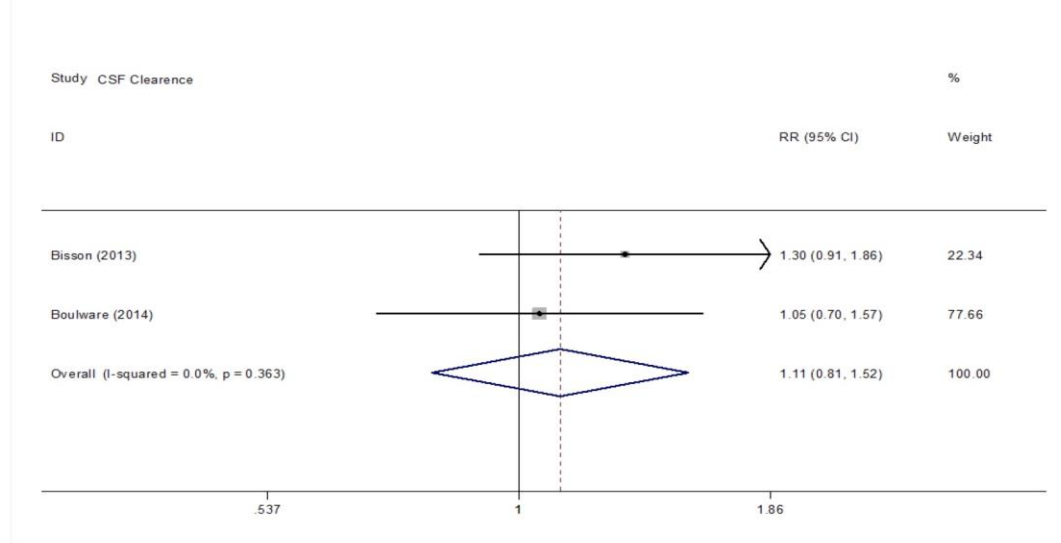
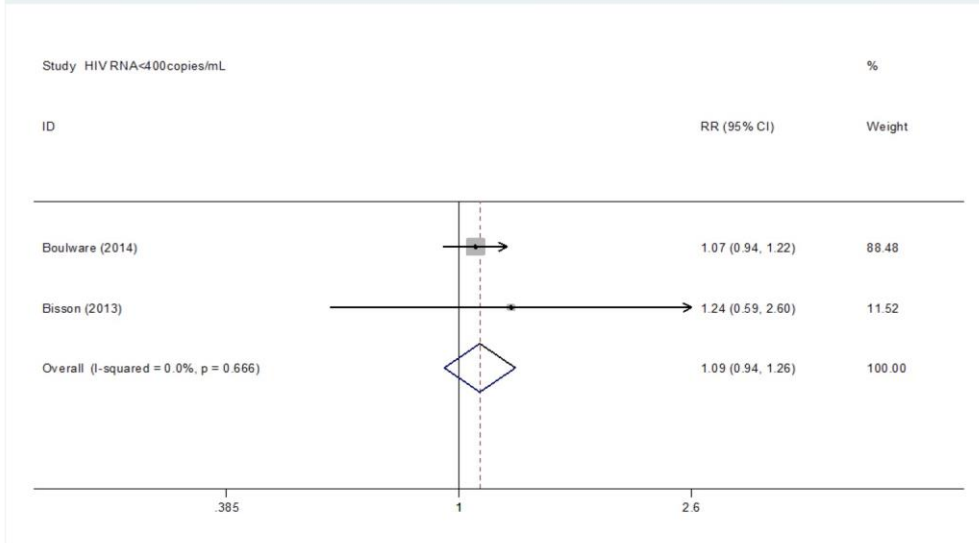
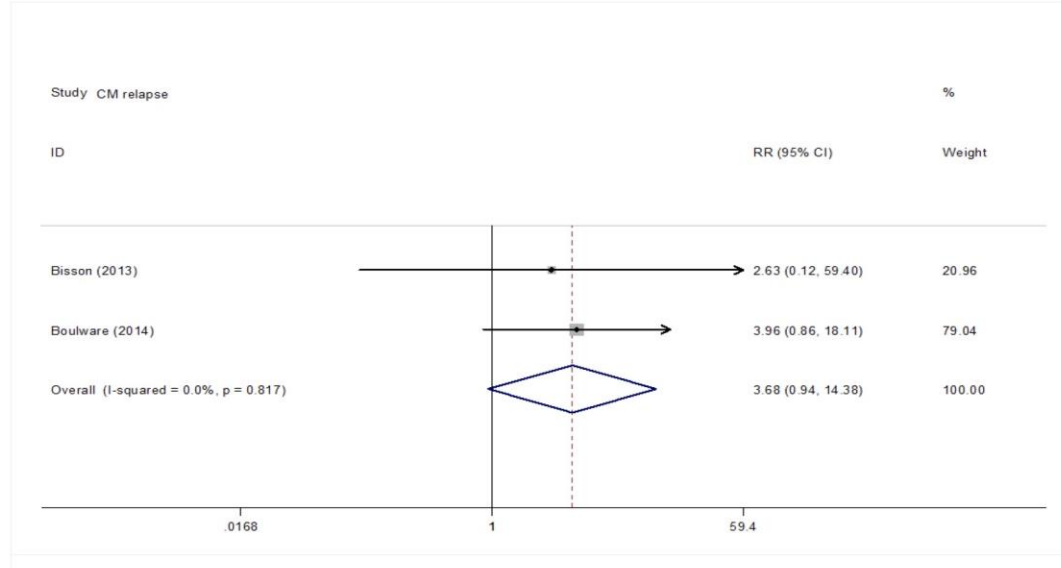
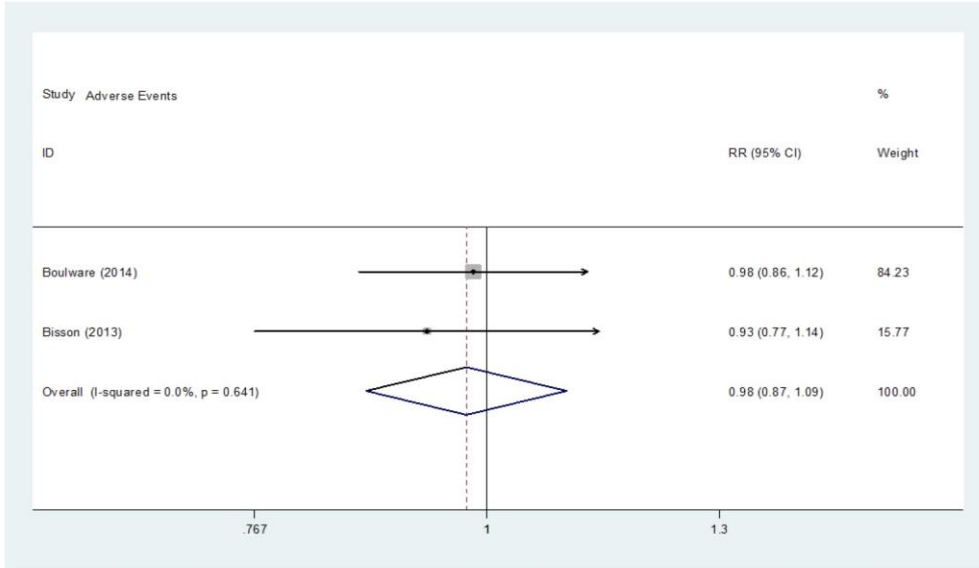


Figure 4. CM-IRIS comparing delayed versus early initiation of ART.





Conclusion

- 1、 Delayed ART initiation in HIV-infected patients with CM improves survival, and is associated with a lower frequency of CM-IRIS.
- 2、 ART initiation should be delayed until the clinical response to the antifungal therapy.



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