NUFFIELD DEPARTMENT OF
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HEALTH SCIENCES

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Does early ART improve survival in adults co-infected with HIV and TB?

Student EBM presentations

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The question

Does early ART improve survival in adults co-infected with HIV and TB?

P	Adults with HIV and TB co-infection
I	Early antiretroviral (ART) treatment
C	Delayed treatment
O	All cause mortality TB-IRIS

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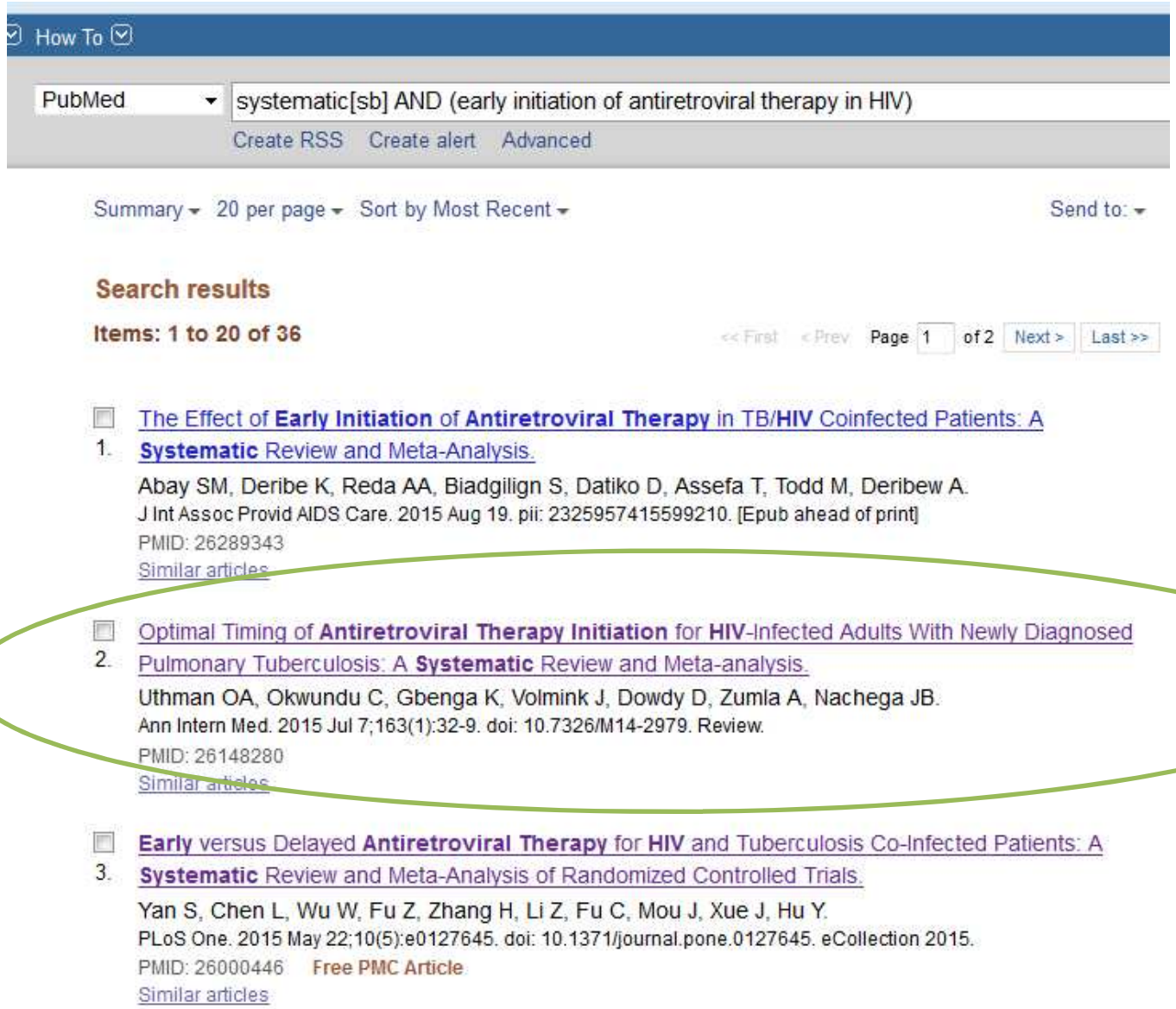
The search and search results



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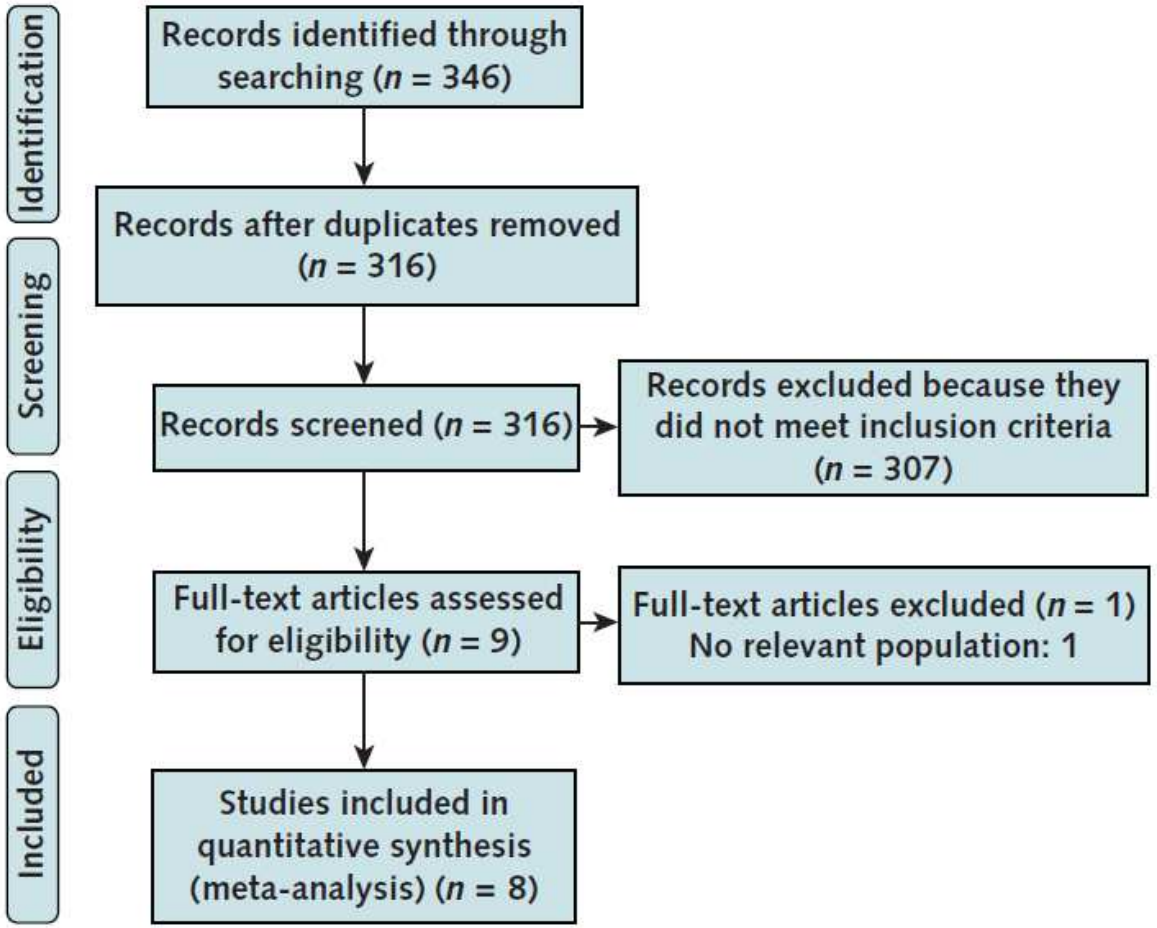
The study appraisal-findings

- PubMed, EMBASE, Cochrane Central Register of Controlled Trials, conference abstracts, and ClinicalTrials.gov (from January 1980 to May 2015)
- Hand searching of journals
- Contacted authors for additional unpublished data for risk of bias assessment
- No language restrictions
- Existing studies on tuberculosis-associated IRIS have used a variety of non-standardised general case definitions

Figure 1. Summary of evidence search and selection.



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The study appraisal-assessment

- 3 authors independently extracted and compared data, risk of bias evaluated across 6 domains using Cochrane collaboration tool

- Discrepancies in bias discussed

- TB treatment and ART comparable in all trials

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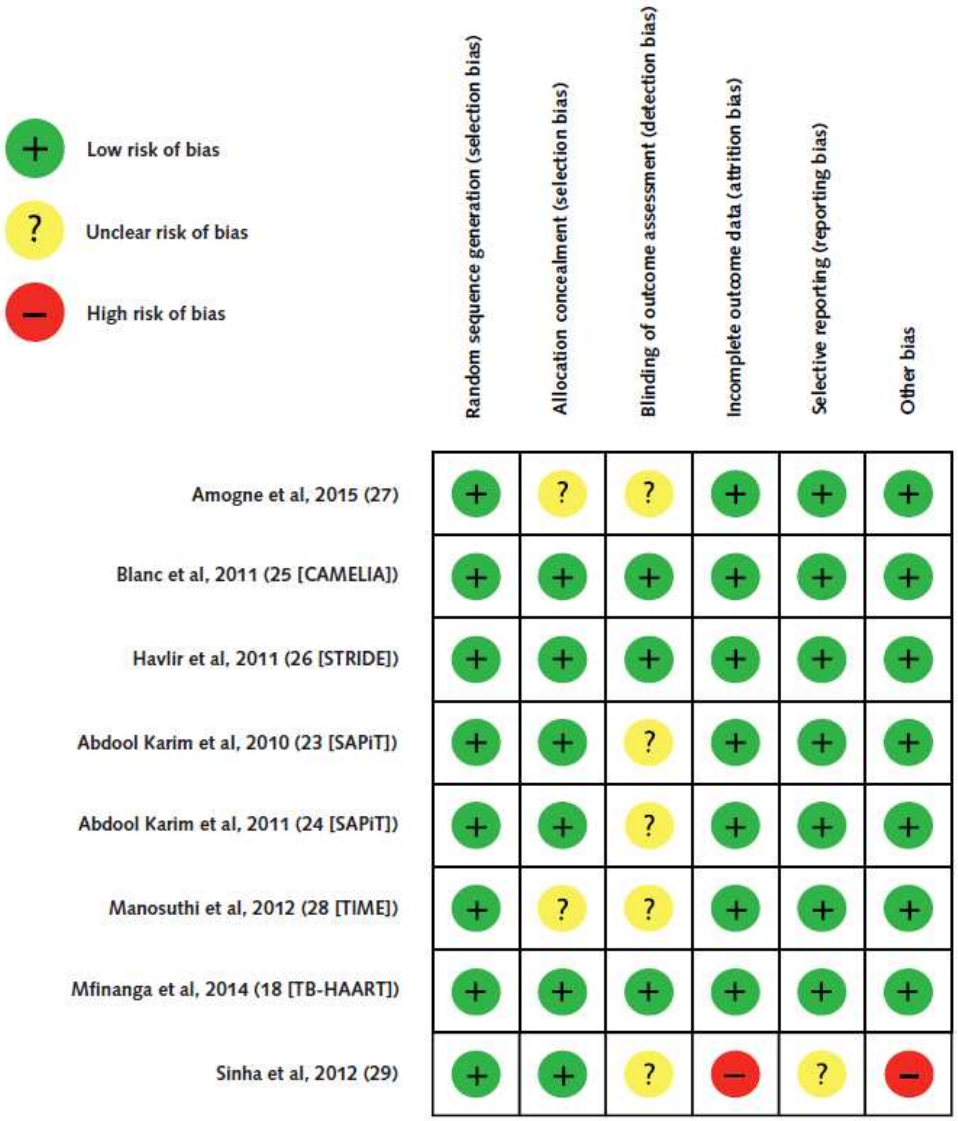
Figure 2. Risk-of-bias assessment of included trials.



CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TB-HAART = An Evaluation of the Impact of Early Initiation of HAART on TB Treatment Outcomes for TB Patients Co-infected With HIV; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

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The Results (interpretation of findings)

- Reduced mortality in early ART group RR0.81 (0.66 to 0.99)
  - CD4+ T cells < 0.05x10^9 RR 0.71 (0.54 to 0.93)
  - CD4+ T cells > 0.05x10^9 RR 1.05 (0.68 to 1.61)
- Increased incidence of TB-IRIS RR 2.31 (1.87 to 2.86)
- 8 trials conducted in Africa, Asia and United States
- Mean age 32-38
- % men varied between 48%-84%
- Loss of follow up more likely in early ART possibly due to increased morbidity from TB-IRIS symptoms
- Incidence of death from TB-IRIS?

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Figure 4. All-cause mortality comparing early versus delayed initiation of ART, stratified by baseline CD4⁺ T-cell counts.

Study, Year (Reference)	Events/Total, *n/N* Early ART	Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
CD4⁺ T-cell counts <0.050 × 10⁹ cells/L				
Amogne et al, 2015 (27)	27/111	10/39	15.2	0.95 (0.51–1.78)
Blanc et al, 2011 (25 [CAMELIA])	48/237	70/238	71.8	0.69 (0.50–0.95)
Abdool Karim et al, 2011 (24 [SAPiT])	3/37	7/35	7.4	0.41 (0.11–1.45)
Manosuthi et al, 2012 (28 [TIME])	4/46	5/38	5.6	0.66 (0.19–2.29)
Subtotal	431	350	100.0	0.71 (0.54–0.93)
Total events	82	92		
Heterogeneity: $X^2 = 1.62$ ($P = 0.66$); $I^2 = 0\%$				
Test for overall effect: $Z = 2.52$ ($P = 0.01$)				
CD4⁺ T-cell counts >0.050 × 10⁹ cells/L				
Amogne et al, 2015 (27)	20/212	7/116	23.9	1.56 (0.68–3.59)
Blanc et al, 2011 (25 [CAMELIA])	11/95	20/91	53.9	0.53 (0.27–1.04)
Abdool Karim et al, 2011 (24 [SAPiT])	12/177	8/180	20.9	1.53 (0.64–3.64)
Manosuthi et al, 2012 (28 [TIME])	2/33	0/39	1.2	5.88 (0.29–118.36)
Subtotal	517	426	100.0	1.05 (0.68–1.61)
Total events	45	35		
Heterogeneity: $X^2 = 6.84$ ($P = 0.08$); $I^2 = 56\%$				
Test for overall effect: $Z = 0.22$ ($P = 0.83$)				
Test for subgroup differences: $X^2 = 2.36$ ($P = 0.12$); $I^2 = 57.7\%$				

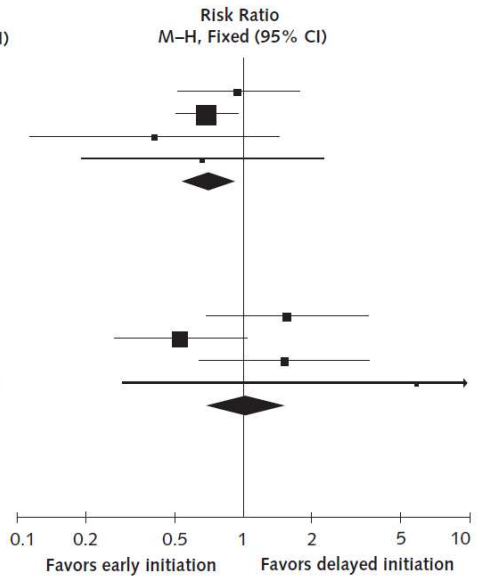
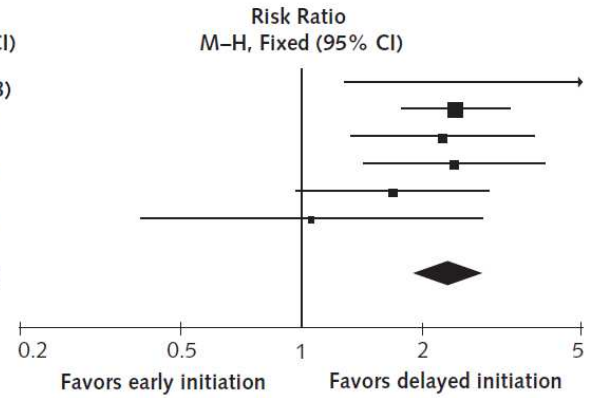


Figure 5. TB-IRIS comparing early versus delayed initiation of ART.

Study, Year (Reference)	Events/Total, *n/N* Early ART	Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
Amogne et al, 2015 (27)	22/332	0/155	0.6	21.08 (1.29–345.28)
Blanc et al, 2011 (25 [CAMELIA])	110/332	45/329	43.0	2.42 (1.77–3.31)
Havlir et al, 2011 (26 [STRIDE])	43/405	19/401	18.2	2.24 (1.33–3.78)
Abdool Karim et al, 2011 (24 [SAPiT])	43/214	18/215	17.1	2.40 (1.43–4.02)
Manosuthi et al, 2012 (28 [TIME])	26/79	15/77	14.4	1.69 (0.97–2.94)
Sinha et al, 2012 (29)	9/88	6/62	6.7	1.06 (0.40–2.82)
Total	1450	1239	100.0	2.31 (1.87–2.86)
Total events	253	103		
Heterogeneity: $X^2 = 6.20$ ($P = 0.29$); $I^2 = 19\%$				
Test for overall effect: $Z = 7.71$ ($P < 0.001$)				



The Implications

- Change WHO guidelines
- Concomitant therapy for TB-IRIS