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HIV合并结核患者CD4$^+$T细胞数、抗逆转录病毒治疗时机选择与结核相关免疫重建炎症综合征关系的Meta分析

李晓亮,李佩珠,林娇如,高仲爱,张　璟　（广东省珠海市慢性病防治中心职业卫生科,广东珠海 519000）

摘　要：目的　系统评价艾滋病合并结核（TB-HIV）患者CD4$^+$T细胞数、抗逆转录病毒疗法（ART）治疗时机选择与结核相关免疫重建炎症综合征（TB-IRIS）的关系。**方法**　检索PubMed和EMBASE数据库1980年1月–2019年12月英文文献,使用R语言Meta程序包V3.3.2进行分析。**结果**　该次分析共纳入10个RCT研究共5 226个研究对象。Meta分析结果显示低CD4$^+$T细胞数和早期ART治疗可增加TB-IRIS发生率。**结论**　CD4$^+$T细胞数和接受ART治疗时机可影响TB-IRIS的发生率。

关键词：CD4$^+$T细胞；抗逆转录病毒疗法；人类免疫缺陷病毒；Meta分析
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Association between CD4$^+$T cells, antiretroviral therapy timing and tuberculosis-associated immune reconstitution inflammatory syndrome in HIV patients with tuberculosis: a Meta analysis

LI Xiao-liang, LI Pei-zhu, LIN Jiao-ru, GAO Zhong-ai, ZHANG Jing (Department of Occupational Health, Zhuhai Center for Chronic Disease Control, Zhuhai 519000, China)

Abstract: Objective　To evaluate the association between CD4$^+$ T cells, antiretroviral therapy (ART) timing and tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with tuberculosis using a Meta analysis. Methods　The English literatures between January 1980 and December 2019 were retrieved on PubMed and

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作者简介：李晓亮（1988–）,男,硕士,主治医师

EMBASE, and analyzed using Meta package V3.3.2 in R. Results　Ten RCT studies and 5,226 objects were included. Meta analysis showed that lower $CD4^+$ T cells and early ART increased incidence of TB-IRIS. Conclusion　$CD4^+$ T cells and ART timing may affect the incidence of TB-IRIS.

Key words: $CD4^+$ T cells; antiretroviral therapy; human immunodeficiency virus; Meta analysis

结核(TB)是艾滋病(HIV)患者最常见的死因之一,大约1/3的HIV患者死因是TB[1]。$CD4^+$T细胞计数>350个/μL且不使用抗逆转录病毒疗法(ART)的艾滋病合并结核(TB-HIV)患者死亡风险在16%~37%[2]。一些在开始结核病治疗的TB-HIV患者中,虽然血浆HIV-RNA水平显著下降、外周血$CD4^+$T细胞计数显著升高,但临床症状却不断加重,这种现象被称作结核相关的免疫重建炎症综合征(TB-IRIS)。WHO目前的指导原则是:$CD4^+$T细胞数<50个/μL时开始抗结核治疗,并在结核治疗开始后的8周内开展ART治疗[3-4]。$CD4^+$T细胞基数达到多少时开始结核治疗,以及是前期还是延后使用ART治疗尚未明确,为此我们开展了本次Meta分析。

1　资料和方法

1.1　资料来源

通过PubMed和EMBASE数据库检索文献,语言限定为英语,时间限定为1980年1月—2019年12月,研究类型限定为RCT,主要研究内容至少包含:低CD4 T细胞基数(<50个/μL)和高CD4 T细胞基数(≥50个/μL)的比较,或前期ART治疗(≤28 d)与延后ART治疗(>28 d)的比较,主要研究结果至少包含TB-IRIS发生率。

1.2　方法

数据由课题组2位成员独立提取,事后比对,不一致时采取双方协商交第三人辅助判定。提取内容包括:研究设计类型、人口学特征以及主要结果指标(TB- IRIS发生率、死亡率)。

1.3　统计学处理

统计软件选用R语言(3.3.2版,"meta"程序包)。通过森林图、tau^2检验以及I^2统计量评估研究的异质性。

2　结果

2.1　基本特征

初步检索文献261篇,经过摘要评估、全文评估排除:研究因为主要结果不包括TB-IRIS被排除(4个)[5-8],研究主要结果不能按低CD4 T细胞基数(<50个/μL)和高$CD4^+$T细胞基数(≥50个/μL)的比较,或前期ART治疗(≤28 d)与延后ART治疗(>28 d)的比较被排除(15个)[9-23];研究和之前研究重复(4个)[24-27]。最终10篇文献纳入本次Meta分析[28-37]。本研究纳入10例的地理范围、研究人数、平均随访时间、年龄、BMI与基线$CD4^+$ T细胞中位数详见表1。

2.2　研究偏倚

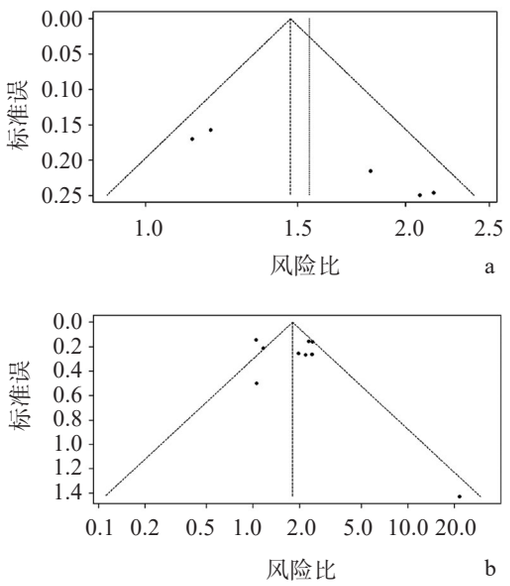
5个比较低$CD4^+$T细胞基数和高$CD4^+$T细胞基数之间的TB-IRIS发生率差异的研究,9个比较前期ART和延后ART治疗之间TB-IRIS发生率差异的研究,见图1。

2.3　异质性

研究的异质性I^2为58%~74%。所有研究异质性不具统计学意义。其中低$CD4^+$T细胞基数患者TB-IRIS发生率是高$CD4^+$T细胞基数患者发生率的1.47

表1　纳入Meta分析的10项研究的基本特征

第一作者	发表年份	国家或地区	研究设计	研究人数	随访年	平均年龄	性别 男/女	基线CD4细胞中位数(个/μL)
Abdool Karim SS	2011	南非	RCT	429	18	34	209/220	152
Havlir DV	2011	美国	RCT	806	48	34	501/305	76
Blanc FX	2011	柬埔寨	RCT	661	50	35	425/236	25
Manosuthi W	2012	泰国	RCT	156	54	38	121/35	45
Sinha S	2012	印度	RCT	150	54	35	126/24	140
Laureillard D	2013	柬埔寨	RCT	597	48	36	385/212	26
Mfinanga SG	2014	南非	RCT	1675	24	32	922/616	367
Amogne W	2015	埃塞俄比亚	RCT	478	8	36	245/233	72
Haridas V	2015	柬埔寨	RCT	154	48	—	—	—
Meintjes G	2018	南非	RCT	120	12	36	73/47	49



a. 纳入低CD4⁺T细胞基数和高CD4⁺T细胞基数之间IRIS-TB比较研究的偏倚；b. 纳入早期ART治疗和延迟ART治疗之间IRIS-TB比较研究的偏倚

图1 研究偏倚评估

倍（R=1.47，95%CI为1.24~1.75，I^2=58%），见图2。

前期ART治疗患者TB-IRIS发生率是延后ART治疗患者发生率的1.80倍（R=1.80，95%CI1.57~2.07，I^2=74%），见图3。

3 讨论

HIV感染者中，TB-HIV双重感染的概率远高于一般人群TB的感染率，联合应用高效抗反转录病毒治疗与抗结核治疗能改善TB-HIV患者的预后。但HIV/AIDS合并TB的治疗复杂，在药物种类、剂量和治疗时机选择及疗程制定等方面均面临诸多问题，如诱发IRIS的发生等。之前，国外众多RCT研究对治疗时机选择及疗程制定进行了评估，但结论并不完全一致。本文在复习文献的基础上，对以上RCT研究进行了Meta分析。

本次研究共纳入10个研究5 226例患者以评估CD4⁺T细胞计数与ART起始时间和TB-IRIS之间的关联。总体来看，CD4⁺T基线细胞数<50个/μL患者的TB-IRIS发生率高于CD4⁺T基线细胞数≥50个/μL患者，之前的研究一般以200个/μL对CD4⁺T细胞进行分组，但是也有以50个/μL进行分组。本研究提示，以50个/μL分组确定治疗时机可能更为合适[38-39]。Muller等[4]研究发现TB-IRIS发病风险与开始ART治疗时的CD4⁺T细胞基数<50个/μL高度相关，本研究结论与其一致；开始结核治疗28 d内进行ART治疗的患者TB-IRIS发生率显著高于开始结核治疗28 d后进行ART治疗者。尽管本次分析结果支持在CD4⁺T基线细胞数<50个/μL采取治疗措施，但是目前的结果尚不能肯定也不能否定开始结核治疗28 d内进行ART治疗者是否能给其生存率带来任何益处。这表明我们需要更多详尽的数据才能更好地定义早期ART的时间阈值。Moher等[40]发现前期ART治疗可以提高结核病和HIV合并感染者的生存率，本次研究结论与其不一致，这可能跟Meta分析时纳入

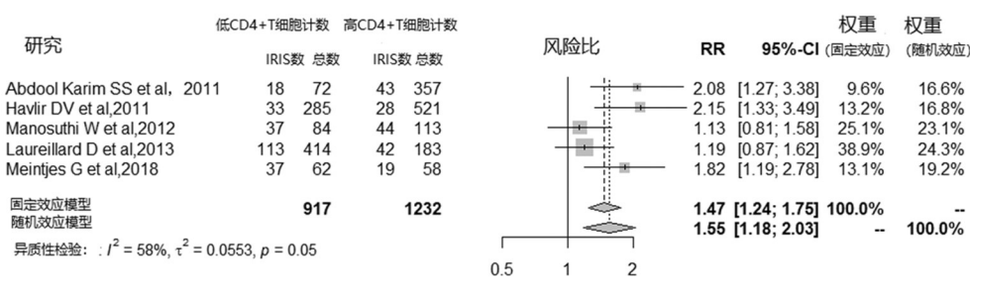


图2 低CD4⁺T细胞基数和高CD4⁺T细胞基数之间IRIS-TB比较

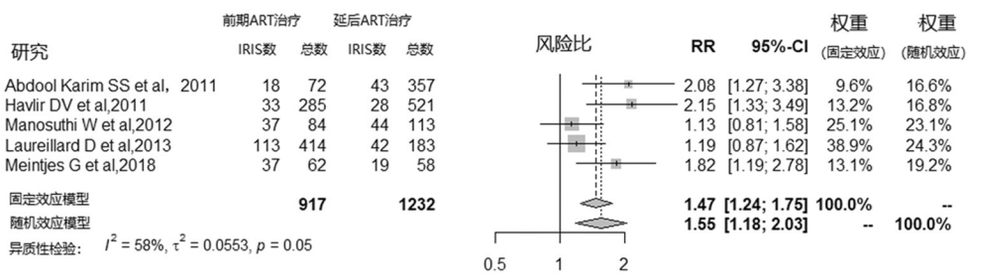


图3 早期ART治疗和延迟ART治疗之间IRIS-TB比较

研究的各组医疗卫生水平不同有关,Meta分析时不可避免地会增加研究对象的异质性,但是这也从侧面说明前期ART治疗是否可以提高结核病和HIV合并感染者的生存率尚不能确定。

除了TB-IRIS发生率,患者全死因死亡率、依从性以及药物交互作用也是研究艾滋病合并结核感染患者需要着重考虑的问题。在南非和其他地区,随着结核病和HIV合并感染越来越普遍,抗炎药(例如糖皮质激素或非甾体类抗炎药)在这些合并感染中的使用越来越广泛,它的实际效果与不良反应需要设计严格的对照试验进一步验证[41]。

本次Meta分析未包含国内研究,结果尚有欠缺,并且个别比较中(如前期ART治疗与晚期ART治疗全死因死亡率的比较)可纳入的RCT较少,仍无法完全避免研究偏倚。尽管存在以上缺陷,本次研究仍能为$CD4^+$T细胞计数和接受ART治疗时机的选择提供参考。

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