抗逆转录病毒疗法治疗艾滋病疗效与安全性的网状Meta分析

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摘要：目的 比较不同抗逆转录病毒疗法的有效性与安全性。**方法** 系统检索国内外抗逆转录病毒治疗艾滋病的随机对照试验，采用Cochrane偏倚风险评估工具评价随机对照试验的质量，使用Stata 17.0软件进行数据分析，效应量采用比值比及95%可信区间表示，并使用累积排序概率曲线下面积值对干预措施进行排序。**结果** 最终纳入36篇随机对照试验，其中19项研究为中低偏倚风险。网状Meta分析结果表明，在抗病毒治疗的短期（48周）和长期（96周）疗效上，基于新型整合酶抑制剂的治疗方案显示出较好疗效。48周时，替诺福韦艾拉酚胺+恩曲他滨+多替拉韦与替诺福韦艾拉酚胺+恩曲他滨+比克替拉韦的病毒抑制率显著优于多个基于非核苷逆转录酶抑制剂或早期蛋白酶抑制剂的传统方案。96周时，基于多替拉韦的方案（包括替诺福韦+恩曲他滨+多替拉韦和阿巴卡韦+拉米夫定+多替拉韦）病毒抑制率显著高于传统方案，并且优于48周的替诺福韦艾拉酚胺+恩曲他滨+多替拉韦方案。不良事件发生率不同方案之间无显著差异。**结论** 替诺福韦艾拉酚胺+恩曲他滨+多替拉韦和替诺福韦+拉米夫定/恩曲他滨+利匹韦林方案有效性和安全性相对较好，可能为艾滋病患者的长期抗病毒治疗提供可靠的方案。

关键词：艾滋病；抗逆转录病毒疗法；网状Meta分析；疗效；安全性；治疗方案；随机对照研究

中图分类号：R512.91；R453 **文献标识码：**A DOI：10.13885/j.issn.2097-681X.M20251045

The comparative efficacy of antiretroviral therapies for acquired immunodeficiency syndrome: a network meta-analysis

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Abstract：Objective To compare the efficacy and safety of different antiretroviral therapy regimens. **Methods** Randomized controlled trialsrelated antiretroviral therapies for acquired immunodeficiency syndrome were systematically retrieved from domestic and international databases. The Cochrane Risk of Bias Tool was used to assess the quality of the randomized controlled trials. Data analysis was per- formed using

收稿日期：2025-07-22 **修回日期：**2025-09-26 **接受日期：**2025-10-11

基金项目：甘肃省科技计划项目（23JRRA1457）；兰州市科技计划项目（2024-9-204，2025-2-28）；兰州市城关区科技计划项目（2024-11-14）；

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Stata 17.0 software, with effect sizes expressed as odds ratios and 95% confidence intervals. Interventions were ranked using the surface under the cumulative ranking curve values. **Results** A total of 36 randomized controlled trials were included, of which 19 studies were assessed as having moder- ate-to-low risk of bias. Network meta-analysis results showed that regimens based on newer integrase strand transfer inhibitors demonstrated significant advantages in both short-term (48-week) and long-term (96-week) antiviral efficacy. At 48 weeks, the tenofovir alafenamide+emtricitabine+dolutegravir and tenofovir alafen-amide+emtricitabine+bictegravir regimens achieved significantly higher viral suppression rates compared to several traditional regimens based on non-nucleoside reverse transcriptase inhibitors or earlier protease inhib- itors. At 96 weeks, DTG-based regimens (including tenofovir disoproxil fumarate+emtricitabine+dolutegravir and abacavir+lamivudine+dolutegravir) showed significantly higher viral suppression rates than traditional regimens and were superior to the 48-week tenofovir alafenamide+emtricitabine+dolutegravir regimen. No significant differences in the incidence of adverse events were observed among the different regimens. **Conclusion** The the tenofovir alafenamide+emtricitabine+dolutegravir and tenofovir disoproxil fumarate+emtricitabine/ lamivudine+rilpivirine regimens demonstrated relatively better efficacy and safety, potentially offering reliable long-term antiviral treatment options for acquired immune deficiency syndrome patients.

Keywords: acquired immunodeficiency syndrome; antiretroviral therapy; network Meta-analysis; efficacy; safeness; therapeutic regimen; randomized controlled trial

抗逆转录病毒疗法（antiretroviral therapy, ART）的出现对于控制人类免疫缺陷病毒（human immunodeficiency virus, HIV）感染进展和获得性免疫缺陷综合征（acquired immunodeficiency syndrome, AIDS）发病率以及AIDS相关死亡率至关重要，极大地提高了艾滋病患者的生活质量[1]。近年来，随着新型长效注射制剂和低毒性药物的研发应用，ART方案选择更加多样化，这些方案在病毒抑制效率、耐药性及药物相关不良反应等方面存在显著差异。尽管已有大量随机对照试验证明各类ART方案的疗效，但临床决策仍面临以下问题：第一，不同药物组合的直接对比证据有限，传统Meta分析难以整合多维度疗效数据，缺乏多药物之间的疗效比较；第二，指南推荐方案受地域、经济、政策的影响，导致药物可及性存在差异；第三，临床实践中医生会根据经验选择方案，可能导致治疗标准化程度不足。

网状Meta分析作为循证医学的重要方法，可突破传统研究的局限性，通过构建间接比较网络，对药物的疗效进行对比，整合结局指标进行多维评估[2]。同时，网状Meta分析还可以实现多种干预措施有效性的优劣排序，帮助临床医生找到最佳的治疗方案，为临床实践提供循证依据[3]。网状Meta分析能够动态整合最新随机对照研究数据，提供高质量的循证证据，为指南修订提供实时证据支持[4]。因此，本研究通过网状Meta分析，探讨艾滋病患者的首选ART方案疗效与安全性，并根据结果对多种ART方案进行排序，进而选择出最优联合药物，以期为医生选择不同治疗方案和制定相关治疗指南提供参考。

1　资料与方法

1.1　资料来源

通过检索中、英文数据库（中国知网、万方、维普、PubMed、Web of Science、Embase等）获得采用ART方案治疗艾滋病的随机对照研究。

中文检索词包括“艾滋病”“获得性免疫缺陷综合征”“随机对照研究”“替诺福韦”（Tenofovir disoproxil fumarate, TDF）、“拉米夫定”（Lamivudine, 3TC）、“恩曲他滨”（Emtricitabine, FTC）、“依非韦伦”（Efavirenz, EFV）、“利匹韦林”（Rilpivirine, RPV）、“洛匹那韦/利托那韦”（Lopinavir/Ritonavir, LPV/r）、“阿扎那韦/利托那韦”（Atazanavir/Ritonavir, ATV/r）、“多替拉韦”（Dolutegravir, DTG）、“拉替拉韦”（Raltegravir, RAL）、“达芦那韦/考比司他”（Darunavir/Cobicistat, DRV/c）、“艾维雷韦/考比司他”（Elvitegravir/Cobicistat, EVG/c）、“多拉韦林”（Doravirine, DOR）、“利托那韦”（Ritonavir, r或

RTV)、“考比司他”(Cobicistat, c)。英文检索词包括“AIDS”“HIV”“acquired immunodeficiency syndrome”“randomised controlled trials”“RCT”“Tenofovir disoproxil fumarate”“Tenofovir alafenamide”“Efavirenz”“Lamivudine”“Efavirenz”“Rilpivirine”“Lopinavir-ritonavir”“Atazanavir-ritonavir”“Dolutegravir”“Raltegravir”“Darunavir-cobicistat”“Elvitegravir-cobicistat”“Doravirine”“Ainuovirin”等相关主题词。以主题词与自由词相结合的方式进行全面检索，检索时限为各数据库建库至2024年12月。详细检索策略以Pubmed数据库检索策略为例，见附表1。

1.2 纳入排除标准

纳入标准：(1)研究人群为既往未接受过治疗的HIV感染者；(2)干预措施包含以下一种或多种核心药物的标准三联ART方案。核心药物包括TDF/TAF、3TC、FTC、EFV、RPV、LPV/r、ATV/r、DTG、RAL、DRV/c、EVG/c、DOR；(3)对照措施为不同治疗方案；(4)中、英文发表的随机对照研究；(5)研究结局包括48周和96周病毒抑制率和不良事件发生率。

排除标准：(1)非原始研究(如会议摘要、评论、综述、系统评价、病例报告、动物实验等)；(2)研究对象合并存在可能显著影响ART疗效或安全性的疾病(如活动性结核病、病毒性肝炎等)。

1.3 文献筛选

将检索记录导入EndNote 20.0软件去除重复记录后，导入Rayyan软件，由两名研究人员独立进行标题和摘要筛选，对符合或潜在符合的文献下载全文并进行全文筛选。筛选过程中存在分歧时，咨询经验丰富的研究人员讨论决定。

1.4 数据提取

两名研究人员根据预先制定的数据提取表独立提取数据，内容包括标题、发表年代、年龄、样本量、基金、CD4细胞计数、HIV-1 RNA病毒载量和结局(病毒抑制率、不良事件发生率)。数据提取过程中若存在分歧，与第三方研究人员讨论解决。

1.5 偏倚风险评估

采用Cochrane偏倚风险工具，从6个领域(选择偏倚、实施偏倚、测量偏倚、随访偏倚、报告偏倚和其他偏倚)对纳入文章进行偏倚风险评估[5]。根据各领域的评估结果判定纳入研究的总体偏倚风险：(1)若所有领域均判定为低风险，则研究的总偏倚风险为“低风险”；(2)若至少一个领域被标记为不清楚并且没有领域被评为高风险，则总偏倚风险为“中风险”；(3)若其中一个或多个领域被判定为高风险，则总偏倚风险为“高风险”[6]。在评价过程中，若存在分歧，交由第三方研究人员讨论解决。

1.6 统计学方法

本研究使用Stata 17.0软件进行贝叶斯网状Meta分析。对于二分类变量结局，采用比值比(odds ratio, *OR*)及相应95%可信区间(confidence interval, *CI*)为效应值；针对有效性结局，当$OR<1$，说明对照组出现阳性结局的优势比大于试验组，即试验组疗效劣于对照组；当$OR=1$，表示试验组和对照组疗效差异无统计学意义；当$OR>1$，则说明试验组出现阳性结局的优势比更高，即试验组疗效优于对照组。针对安全性结局，当$OR<1$，表明试验组发生不良事件的优势比低于对照组，试验组安全性更好；当$OR=1$，说明安全性差异无统计学意义；当$OR>1$，表明试验组发生不良事件的优势比大于对照组，试验组安全性相对较差。对连续性变量，采用标准化均数差(standardized mean difference, *SMD*)或均数差(mean difference, *MD*)及相应的95% *CI*作为效应值。当$P<0.05$时认为差异有统计学意义。使用网络证据图来表示各结局中干预措施之间的关系。通过累积排序概率曲线下面积(surface under the cumulative ranking curve, SUCRA)对不同ART方案的效果进行排序，SUCRA越接近100%，表示某种干预措施治疗效果更优的可能性越大。最后采用比较—校正漏斗图评估是否存在发表偏倚[6]。当网状Meta分析存在闭合环时，对闭合环进行网状不一致性检验，若$P>0.05$，即闭合环内直接证据和间接证据一致性较好，说明网状结构稳固[7]。

2　结果

2.1　文献筛选结果

检索共获得6 364篇文献。去除1 414条重复记录后，对剩余的4 950条记录通过阅读题目和摘要筛选，筛选出173条符合或/和潜在符合的记录。对173条记录进行全文筛选，排除137条记录，最终纳入36篇随机对照研究[8-43]，文献筛选流程见图1。

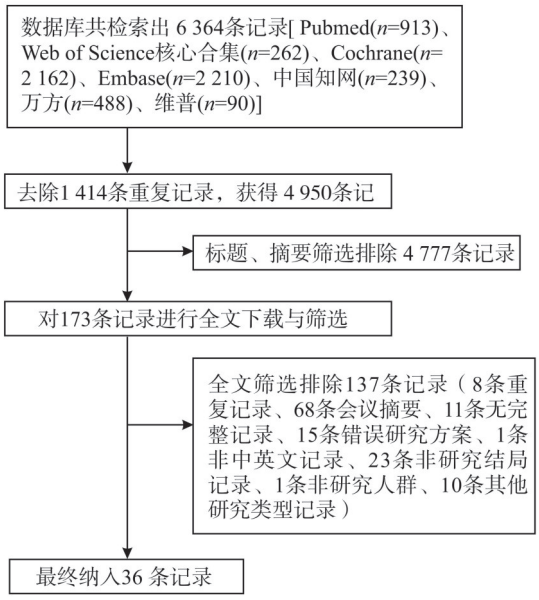


图1　文献筛选流程

2.2　纳入文献基本特征

纳入36篇随机对照研究，共20 604人。研究样本由36人到1 733人不等。纳入文献中，共有19种ART方案。80.5%的研究均报告了干预措施的男女比例，基线资料相似具有可比性，且干预措施均为指南中提及的首选ART方案，详见表1。

表1　纳入研究基本特征表

第一作者	治疗措施	n	$n_{治疗}$	$n_{男}/n_{女}$	每毫升血液中经过对数转换的HIV病毒遗传物质（RNA或DNA）的拷贝数	每立方毫米血液中CD4细胞计数/个	结局指标
Molina J M[8]	ATV/r/FTC/TDF	833	440	302/138	4.56	365	①④⑥
	LPV/r/FTC/TDF		443	304/139	4.69	343	
Ortiz R[9]	DRV/r/FTC/TDF	689	343	239/104	4.85	225	①③④⑤
	LPV/r/FTC/TDF		346	241/105			
Lennox J L[10]	RAL/FTC/TDF	563	281	227/54	4.85	228	①③④
	EFV/FTC/TDF		282	231/51	4.79	218	⑤⑥
Markowitz M[11]	RAL/3TC/TDF	198	160	/	4.70	305	①④
	EFV/3TC/TDF		38	/	4.80	280	⑤⑥
Mills A M[12]	DRV/r/FTC/TDF	689	343	239/104	4.98	205	②③④⑤
	LPV/r/FTC/TDF		346	241/105			
Molina J M[13]	ATV/r/FTC/TD	833	440	302/138	4.98	205	②④⑥
	LPV/r/FTC/TDF		443	304/139			
Lennox J L[14]	RAL/FTC/TDF	563	281	227/54	5.0±0.6	219±124	①②④
	EFV/FTC/TDF		282	231/51	5.0±0.6	217±134	⑤⑥
Soriano V[15]	NVP/TDF/FTC	569	376	315/61	5.1±0.6	184±96	①⑤⑥
	ATV/r/TDF/FTC		193	162/31			
Cohen C[16]	EVG/c/FTC/TDF	71	48	44/4	4.59	354	①⑥
	EFV/FTC/TDF		23	21/2	4.58	436	
Dejesus E[17]	NVP/TDF/FTC	152	75	65/10	4.46[a]	344[a]	①④
	ATV/r/FTC/TDF		77	71/6	4.56[a]	370[a]	⑤⑥
DeJesus E[18]	EVG/c/FTC/TDF	708	353	324/29	5[a]	218.9	①④
	ATV/r+FTC/TDF		355	316/39	5[a]	217.4	
Walmsley S L[19]	DTG-ABC-3TC	833	414	347/67	4.68[a]	338[a]	①③④⑤⑥
	EFV-TDF-FTC		419	356/63			
Cohen C[20]	RPV/FTC/TDF	786	394	366/28	4.43	440	①③⑤
	EFV/FTC/TDF		392	364/28	4.45	441	
Sax P E[21]	EVG/c/FTC/TAF	170	112	108/4	4.61	385	①④⑤
	EVG/c/FTC/TDF		58	57/1		397	
Sax P E[22]	EVG/c+FTC/TAF	1 733	866	733/133	4.58	404	①
	EVG/c+FTC/TDF		867	740/127	4.58	406	

续表

第一作者	治疗措施	n	$n_{治疗}$	$n_{男}/n_{女}$	每毫升血液中经过对数转换的HIV病毒遗传物质(RNA或DNA)的拷贝数	每立方毫米血液中CD4细胞计数/个	结局指标
Walmsley S[23]	DTG-ABC-3TC	833	414	347/67	4.68[a]	3 381	②④
	EFV-TDF-FTC		419	356/63			⑤⑥
Miro J M[24]	EFV+FTC/TDF	89	29	21/8	/	32	①④
	ATV/r+FTC/TDF		30	27/3			⑤⑥
	LPV/r+FTC/TDF		30	25/5			
Mills A[25]	DRV/c/FTC/TAF	153	103	95/8	4.70	384	①④⑤
	DRV/c+FTC/TDF		50	47/3			
van Lunzen J[26]	RPV/FTC/TDF	786	394	/	4.8±0.61	351	①③④
	EFV/FTC/TDF		392	/	4.8±0.62	366	⑤⑥
Squires K[27]	EVG/c/FTC/TDF	575	289	/	5.17[a]	547[a]	①⑤⑥
	ATV/r+FTC/TDF		286	/	5.43[a]	552[a]	
Sax P E[28]	BIC/FTC/TAF	98	65	64/1	4.451	4 441	①④
	DTG/FTC/TAF		33	30/3			
Gallant J[29]	BIC/FTC/TAF	629	314	285/29	4.42	443	①④
	DTG/ABC/3TC		315	282/33	4.51	450	⑤⑥
Gallant J[30]	ATV/c+FTC/TDF	692	344	287/57	4.8±0.7	396±180	①④
	ATV/r+FTC/TDF		348	287/61	4.8±0.6	385±187	
Elion R[31]	BIC/FTC/TAF	645	320	280/40	4.8±0.6	391±183	①④⑥
	DTG/FTC/TAF		325	288/37			
Orrell C[32]	DTG/ABC/3TC	495	248	/	4.41	340	①③④
	ATV/r +TDF/FTC		247	/	4.43	350	⑤⑥
Eron J J[33]	DRV/c+FTC/TDF	725	362	318/44	4.52[a]	453[a]	①③④
	DRV/c+FTC/TAF		363	322/41			⑤⑥
Orkin C[34]	DOR/3TC/TDF	728	364	305/59	4.4[a]	397[a]	①④
	EFV/FTC/TDF		364	311/53			⑤⑥
Venter W D F[35]	DTG/FTC/TAF	1 053	351	/	/	/	②④⑤
	DTG+FTC/TDF		351	/			
	EFV/FTC/TDF		351	/			
Cahn P[36]	DTG + 3TC	1 433	716	603/113	4.42	462.0	②③④
	DTG + TDF/FTC		717	619/98	4.45	461.3	⑤⑥
Orkin C[37]	DOR/3TC/TDF	728	364	305/59	4.4[a]	397[a]	②③④
	EFV/FTC/TDF		364	311/53			⑤⑥
Podzamczer D[38]	DRV/c/FTC/TAF	306	151	146/5	/	/	①④⑥
	DTG-ABC-3TC		155	142/13			
Bruzzesi E[39]	DRV/c/FTC/TAF	58	30	26/3/1[b]	/	/	①
	DTG/FTC/TAF		28	28/0/0[b]	/	/	
Su B[40]	ANV/3TC/TDF	630	315	/	4.48±0.651	380.4±183.6	①③
	EFV/3TC/TDF		315	/			④⑤
Whitlock G[41]	BIC/FTC/TAF	36	19	19/0	4.79±0.87	505±253	①④
	DRV/c/FTC/TAF		17	15/2			⑤⑥
Wang R[42]	EFV-3TC-TDF	295	149	/	4.5[a]	334[a]	①④
	BIC/FTC/TAF		146	/	4.4[a]	340[a]	⑤⑥
Cordova E[43]	DTG+3TC	214	106	82/24	/	/	①
	TDF+XTG+DTG		108	83/25			

HTV 人类免疫缺陷病毒。① 48周病毒抑制，② 96周病毒抑制，③ 亚组分析，④ 不良事件，⑤ 严重不良事，⑥ 药物相关不良事件。ATV 阿扎那韦，r 利托那韦，FTC 恩曲他滨，TDF 替诺福韦，LPV 洛匹那韦，DRV 达芦那韦，RAL 拉替拉韦，EFV 依非韦伦，3TC 拉米夫定，NVP 奈韦拉平，EVG 埃替格韦，c 考比司他，DTG 多替拉韦，ABC 阿巴卡韦，TAF 丙酚替诺福韦，RPV 利匹韦林，BIC 比克替拉韦，DOR 多拉韦林，ANV 艾诺韦林，XTC 拉米夫定/恩曲他滨。a 基线DNA，b 变性者。

2.3　偏倚风险评估

纳入36篇研究均存在不同程度的偏倚风险。其中，12项随机对照试验为低偏倚风险，7项为中偏倚风险，17项为高偏倚风险。高偏倚风险产生的主要原因在于试验过程中未实施盲法，且采用开放标签的方式开展研究和未能清晰阐述随机分配的具体过程。所有纳入研究的结局均严格按照预先设定的研究方案进行分析，同时，并未发现有其他偏倚风险的情况。偏倚风险评估汇总结果见图2。

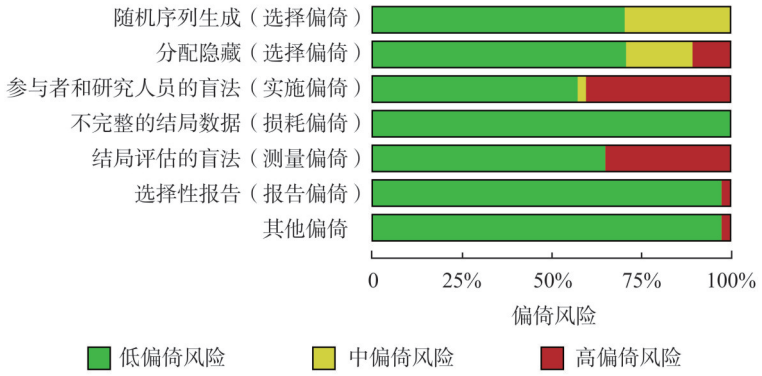
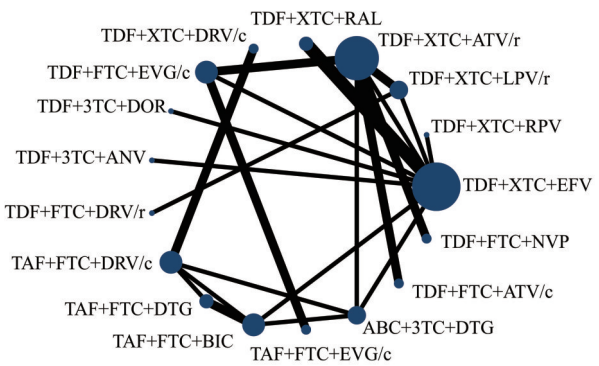


图2　偏倚风险评估结果

3　网状Meta分析结果

3.1　抗病毒疗效

HIV RNA<50 拷贝数/mL是反映ART疗效的主要结局指标[44]，29项研究报告了48周时HIV RNA<50拷贝数/mL的人数，涉及17种ART方案。不一致性检验显示差异无统计学意义（P>0.05）。网状证据图显示TDF+XTC+EFV和TDF+XTC+RAL是被连接次数最多的方案（图3）。网状Meta分析结果显示含整合酶抑制剂如DTG、BIC的方案，以及含DRV/c方案，表现出优于传统方案的趋势。具体而言，与新型含整合酶抑制剂方案（TAF+FTC+DTG）相比，一些传统方案如TDF+XTC+EFV（OR=0.34, 95% CI:[0.17,0.70]）和TDF+XTC+LPV/r（OR=0.34，95% CI:[0.15，0.76]）的病毒抑制率较低。多种新方案表现出卓越疗效，例如，TAF+FTC+DTG（OR=3.27，95% CI: [1.38，7.78]）和ABC+3TC+DTG（OR=2.27，95% CI: [1.29，3.99]）的病毒抑制率显著优于TDF+FTC+ATV/c方案。不同ART方案之间的两两比较结果见表2。48周病毒抑制率排序结果显示前三位的方案依次为TAF+FTC+DTG、TDF+XTC+DRV/c和TAF+FTC+BIC（附表2）。



TDF　替诺福韦，3TC　拉米夫定，FTC　恩曲他滨，EFV　依非韦伦，RPV　利匹韦林，LPV/r　洛匹那韦/利托那韦，ATV/r　阿扎那韦/利托那韦，DTG　多替拉韦，RAL　拉替拉韦，DRV/c　达芦那韦/考比司他，EVG/c　艾维雷韦/考比司他，DOR 多　拉韦林，r或RTV　利托那韦。

图3　48周病毒抑制率网络关系图

6项研究报告了96周时HIV RNA<50拷贝数/mL的人数，涉及8种ART方案。不一致性检验显示差异无统计学意义（P>0.05）。网状证据图显示TDF+XTC+EFV是被连接次数最多的治疗方案，TDF+XTC+DTG是连接次数第二的治疗方案（附图1）。网状Meta分析结果显示：TDF+XTC+EFV（OR=0.65，95% CI:[0.47，0.89]）的病毒抑制率较ABC+3TC+DTG方案差。TDF+XTC+DTG（OR=1.39，95% CI:[1.01，1.91]）的病毒抑制率较DTG+3TC方案好，差异具有统计学意义（P<0.05），详见附表3。96周病毒抑制率排序结果显示前三位的方案依次为：ABC+3TC+DTG、TDF+XTC+RPV、TAF+FTC+DTG（附表4）。

表2 48周病毒抑制率列联表

TDF+XTC+EFV																
0.74 (0.50, 1.08)	TDF+XTC+RPV															
1.02 (0.60, 1.74)	1.38 (0.72, 2.67)	TDF+XTC+LPV/r														
0.92 (0.58, 1.46)	1.25 (0.68, 2.28)	0.90 (0.67, 1.22)	TDF+XTC+ATV/r													
0.87 (0.66, 1.14)	1.18 (0.74, 1.88)	0.85 (0.47, 1.55)	0.94 (0.55, 1.62)	TDF+XTC+RAL												
0.38 (0.18, 0.79)	0.51 (0.22, 1.18)	0.37 (0.16, 0.84)	0.41 (0.19, 0.89)	0.44 (0.20, 0.96)	TDF+XTC+DRV/c											
0.62 (0.36, 1.07)	0.84 (0.43, 1.63)	0.61 (0.39, 0.94)	0.67 (0.49, 0.92)	0.71 (0.39, 1.31)	1.64 (0.72, 3.73)	TDF+FTC+EVG/c										
0.78 (0.53, 1.15)	1.06 (0.62, 1.82)	0.77 (0.40, 1.48)	0.85 (0.46, 1.55)	0.90 (0.56, 1.44)	2.07 (0.90, 4.76)	1.26 (0.65, 2.45)	TDF+3TC+DOR									
1.66 (0.99, 2.78)	2.25 (1.18, 4.28)	1.63 (0.77, 3.43)	1.80 (0.90, 3.62)	1.91 (1.07, 3.43)	4.39 (1.78, 10.84)	2.68 (1.26, 5.68)	2.13 (1.11, 4.05)	TDF+3TC+ANV								
0.89 (0.46, 1.74)	1.21 (0.56, 2.61)	0.87 (0.59, 1.30)	0.97 (0.59, 1.60)	1.03 (0.50, 2.12)	2.36 (0.95, 5.87)	1.44 (0.80, 2.60)	1.14 (0.53, 2.47)	0.54 (0.23, 1.25)	TDF+FTC+DRV/r							
0.54 (0.30, 0.99)	0.74 (0.36, 1.51)	0.53 (0.27, 1.07)	0.59 (0.31, 1.12)	0.63 (0.32, 1.21)	1.4 (0.94, 2.21)	0.88 (0.43, 1.78)	0.70 (0.34, 1.43)	0.33 (0.15, 0.73)	0.61 (0.27, 1.36)	TAF+FTC+DRV/c						
0.34 (0.17, 0.70)	0.46 (0.21, 1.04)	0.34 (0.15, 0.76)	0.37 (0.17, 0.80)	0.39 (0.18, 0.84)	0.91 (0.38, 2.15)	0.55 (0.24, 1.25)	0.44 (0.20, 0.98)	0.21 (0.09, 0.50)	0.38 (0.16, 0.95)	0.63 (0.30, 1.33)	TAF+FTC+DTG					
0.40 (0.23, 0.67)	0.54 (0.28, 1.03)	0.39 (0.20, 0.75)	0.43 (0.24, 0.78)	0.46 (0.25, 0.82)	1.05 (0.49, 2.23)	0.64 (0.33, 1.24)	0.51 (0.26, 0.97)	0.24 (0.11, 0.50)	0.44 (0.21, 0.96)	0.73 (0.39, 1.35)	1.16 (0.69, 1.93)	TAF+FTC+BIC				
0.50 (0.27, 0.93)	0.68 (0.32, 1.41)	0.49 (0.29, 0.84)	0.54 (0.35, 0.85)	0.57 (0.29, 1.14)	1.32 (0.55, 3.19)	0.80 (0.59, 1.10)	0.64 (0.31, 1.33)	0.30 (0.13, 0.68)	0.56 (0.29, 1.09)	0.92 (0.42, 1.98)	1.45 (0.61, 3.49)	1.26 (0.60, 2.63)	TAF+FTC+EVG/c			
0.49 (0.35, 0.69)	0.67 (0.40, 1.12)	0.48 (0.30, 0.78)	0.54 (0.37, 0.79)	0.57 (0.37, 0.88)	1.31 (0.67, 2.55)	0.80 (0.49, 1.30)	0.63 (0.38, 1.06)	0.30 (0.16, 0.55)	0.55 (0.30, 1.03)	0.91 (0.54, 1.52)	1.44 (0.74, 2.81)	1.25 (0.78, 2.00)	0.99 (0.56, 1.77)	ABC+3TC+DTG		
1.12 (0.60, 2.09)	1.52 (0.73, 3.15)	1.10 (0.66, 1.83)	1.22 (0.81, 1.84)	1.29 (0.66, 2.55)	2.97 (1.24, 7.10)	1.81 (1.08, 3.04)	1.44 (0.69, 2.98)	0.68 (0.30, 1.52)	1.26 (0.66, 2.40)	2.06 (0.96, 4.40)	3.27 (1.38, 7.78)	2.83 (1.37, 5.85)	2.25 (1.23, 4.13)	2.27 (1.29, 3.99)	TDF+FTC+ATV/c	
0.91 (0.52, 1.60)	1.23 (0.62, 2.44)	0.89 (0.57, 1.38)	0.99 (0.72, 1.36)	1.05 (0.56, 1.96)	2.40 (1.05, 5.53)	1.47 (0.93, 2.30)	1.16 (0.59, 2.30)	0.55 (0.25, 1.18)	1.02 (0.56, 1.84)	1.67 (0.82, 3.41)	2.65 (1.16, 6.05)	2.29 (1.16, 4.52)	1.82 (1.05, 3.15)	1.84 (1.11, 3.03)	0.81 (0.48, 1.36)	TDF+FTC+NVP

本表格为下三角矩阵，每个单元格内的数值代表行治疗方案相对于列治疗方案的比值比（*OR*）及其95%可信区间。*OR*>1表示行治疗方案的病毒抑制效果优于列治疗方案；*OR*<1则表示行治疗方案的病毒抑制效果劣于列治疗方案。黑色加粗的数值代表该比较差异具有统计学意义（$P<0.05$）。TDF 替诺福韦，XTC 拉米夫定/恩曲他滨，EFV 依非韦伦，TDF 替诺福韦，RPV 利匹韦林，LPV 洛匹那韦，r 利托那韦，ATV 阿扎那韦，RAL 拉替拉韦，DRV 达芦那韦，c 考比司他，3TC 拉米夫定，DOR 多拉韦林，ANV 艾诺韦林，FTC 恩曲他滨，TAF 丙酚替诺福韦，FTC 恩曲他滨，EVG 埃替格韦，ABC 阿巴卡韦，DTG 多替拉韦，NVP 奈韦拉平。

3.2　安全性

21项研究报告了48周不良事件发生率，涉及16种ART方案。不一致性检验结果显示差异无统计学意义（$P>0.05$）。网状证据图显示TDF+XTC+EFV、TDF+XTC+ATV/r是被连接次数最多的治疗方案（附图2）。TDF+XTC+EFV不良事件发生率高于TDF+XTC+RAL（$OR=2.79$，95% CI：[1.05，7.42]）和ABC+3TC+DTG（$OR=2.28$，95% CI：[1.05，4.94]）。其他各联合药物之间差异无统计学意义（$P>0.05$），详见表3。48周不良事件发生率排序前三位方案依次为：TDF+FTC+NVP、TDF+FTC+EVG/c、TAF +FTC+EVG/c（附表5）。

共有5项研究报告了96周不良事件发生率，涉及7种ART方案。网状证据图显示TDF+XTC+

表3　48周不良事件发生率列联表

TDF+XTC+EFV															
1.55 (0.42, 5.74)	TDF+XTC+LPV/r														
2.34 (0.78, 7.02)	1.51 (0.61, 3.75)	TDF+XTC+ATV/r													
2.79 (1.05, 7.42)	1.80 (0.35, 9.27)	1.19 (0.27, 5.25)	TDF+XTC+RAL												
1.90 (0.35, 10.45)	1.23 (0.17, 8.77)	0.81 (0.13, 4.93)	0.68 (0.09, 5.03)	TDF+XTC+DRV/c											
3.27 (0.59, 18.03)	2.11 (0.43, 10.35)	1.40 (0.38, 5.16)	1.17 (0.16, 8.47)	1.72 (0.19, 15.90)	TDF+FTC+EVG/c										
2.03 (0.63, 6.56)	1.31 (0.23, 7.58)	0.87 (0.17, 4.33)	0.73 (0.16, 3.35)	1.07 (0.14, 8.42)	0.62 (0.08, 4.93)	TDF+3TC+DOR									
2.42 (0.69, 8.57)	1.56 (0.25, 9.62)	1.04 (0.19, 5.52)	0.87 (0.18, 4.30)	1.27 (0.15, 10.60)	0.74 (0.09, 6.20)	1.19 (0.21, 6.68)	TDF+3TC+ANV								
3.11 (0.52, 18.81)	2.01 (0.58, 6.89)	1.33 (0.29, 6.17)	1.12 (0.14, 8.72)	1.63 (0.16, 16.68)	0.95 (0.13, 7.14)	1.53 (0.18, 13.11)	1.28 (0.14, 11.57)	TDF+FTC+DRV/r							
2.27 (0.56, 9.26)	1.46 (0.26, 8.13)	0.97 (0.21, 4.45)	0.81 (0.14, 4.70)	1.19 (0.45, 3.13)	0.69 (0.09, 5.16)	1.12 (0.18, 6.96)	0.94 (0.14, 6.20)	0.73 (0.09, 6.04)	TAF+FTC+DRV/c						
2.95 (0.57, 15.20)	1.90 (0.28, 13.00)	1.26 (0.22, 7.30)	1.06 (0.16, 7.12)	1.55 (0.20, 11.75)	0.90 (0.10, 8.06)	1.45 (0.19, 10.90)	1.22 (0.15, 9.65)	0.95 (0.10, 9.31)	1.30 (0.22, 7.75)	TAF+FTC+DTG					
2.85 (0.71, 11.38)	1.83 (0.33, 10.23)	1.22 (0.26, 5.64)	1.02 (0.19, 5.38)	1.50 (0.23, 9.58)	0.87 (0.12, 6.53)	1.40 (0.23, 8.61)	1.18 (0.18, 7.66)	0.91 (0.11, 7.59)	1.26 (0.25, 6.19)	0.96 (0.38, 2.46)	TAF+FTC+BIC				
3.39 (0.29, 40.23)	2.19 (0.20, 23.97)	1.45 (0.16, 13.29)	1.22 (0.08, 17.52)	1.78 (0.10, 30.98)	1.04 (0.17, 6.21)	1.67 (0.11, 25.78)	1.40 (0.09, 22.50)	1.09 (0.07, 16.13)	1.50 (0.10, 22.03)	1.15 (0.07, 19.42)	1.19 (0.08, 17.62)	TAF+FTC+EVG/c			
2.28 (1.05, 4.94)	1.47 (0.41, 5.20)	0.97 (0.36, 2.63)	0.82 (0.23, 2.86)	1.19 (0.26, 5.41)	0.70 (0.13, 3.60)	1.12 (0.27, 4.57)	0.94 (0.21, 4.14)	0.73 (0.12, 4.29)	1.00 (0.31, 3.22)	0.77 (0.18, 3.27)	0.80 (0.25, 2.53)	0.67 (0.06, 7.61)	ABC+3TC+DTG		
2.38 (0.47, 11.96)	1.53 (0.34, 6.82)	1.02 (0.31, 3.32)	0.85 (0.13, 5.70)	1.25 (0.14, 10.79)	0.73 (0.12, 4.24)	1.17 (0.16, 8.61)	0.98 (0.13, 7.63)	0.76 (0.11, 5.30)	1.05 (0.15, 7.23)	0.81 (0.10, 6.70)	0.84 (0.12, 5.79)	0.70 (0.06, 8.64)	1.05 (0.22, 4.91)	TDF+FTC ATV/c	
5.82 (0.81, 41.77)	3.75 (0.58, 24.37)	2.49 (0.49, 12.76)	2.09 (0.23, 19.02)	3.06 (0.27, 34.86)	1.78 (0.22, 14.44)	2.87 (0.29, 28.38)	2.40 (0.23, 24.96)	1.87 (0.20, 17.61)	2.57 (0.27, 24.02)	1.97 (0.18, 21.74)	2.05 (0.22, 19.24)	1.72 (0.11, 26.95)	2.56 (0.38, 17.36)	2.45 (0.33, 18.42)	TDF/FTC+NVP

本表格为下三角矩阵，每个单元格内的数值代表行治疗方案相对于列治疗方案的比值比（OR）及其95%置信区间。$OR>1$表示行治疗方案的不良事件发生率大于列治疗方案；$OR<1$则表示行治疗方案的不良事件发生率小于列治疗方案。黑色加粗的数值代表该比较差异具有统计学意义（$P<0.05$）。TDF　替诺福韦，XTC　拉米夫定/恩曲他滨，EFV　依非韦伦，TDF　替诺福韦，RPV　利匹韦林，DTG　多替拉韦，RAL　拉替拉韦，3TC　拉米夫定，DOR　多拉韦林，TAF　丙酚替诺，FTC　恩曲他滨，ABC　阿巴卡韦。

EFV是被连接次数最多的治疗方案（附图3）。网状Meta分析结果显示：TDF+XTC+EFV不良事件发生率高于TAF+FTC+DTG（*OR*=5.12，95% *CI*：[1.11，23.53]）、ABC+3TC+DTG（*OR*=2.64,95% *CI*：[1.99，3.50]）、TDF+FTC+DTG（*OR*=10.26,95% *CI*：[1.31，80.58]）和DTG+3TC（*OR*=12.24，95% *CI*：[1.53，97.96]）；TDF+XTC+RPV不良事件发生率高于ABC+3TC+DTG（*OR*=1.94,95% *CI*:[1.05，3.61]）和DTG+3TC（*OR*=9.03，95% *CI*：[1.05，77.61]）两种联合方案，其他各方案间差异无统计学意义（*P*>0.05），详见附表6。96周不良事件发生率排序前三位的方案依次为DTG+3TC、TDF+FTC+DTG和TAF+FTC+DTG（附表7）。

3.3 发表偏倚

48周病毒抑制率和48周不良事件发生率的漏斗图节点呈现不对称分布，表明存在一定程度的发表偏倚（附图4A、4B），而96周病毒抑制率和96周不良事件发生率的漏斗图节点分布对称，表明存在发表偏倚的可能性较小（附图4C、4D）。

4 讨论

本研究共纳入36篇随机对照试验，通过网状Meta方法评估指南中提及的首选ART药物的疗效和安全性，利用SUCRA对药物进行优劣排序。网状Meta分析结果显示，48周病毒抑制率疗效排名前三的联合药物是TAF+FTC+DTG、TDF+XTC+DRV/c、TAF+FTC+BIC；96周病毒抑制率疗效排名前三的联合药物是TDF+FTC+DTG、TDF+XTC+RAL、ABC+3TC+DTG；48周不良事件发生率较低排名前三的联合药物是TDF+FTC+NVP、TDF+FTC+EVG/c、TAF+FTC+EVG/c；96周不良事件发生率较低排名前三的联合药物是DTG+3TC、TDF+FTC+DTG、TAF+FTC+DTG。

TAF+FTC+DTG在48周病毒抑制率结局中疗效好，TDF+FTC+DTG在96周病毒抑制率中疗效好，这一结果与既往研究存在一致性。ADVANCE试验（糖尿病与血管疾病行动研究）[45]表明，全球大多数HIV感染者目前都在接受含有DTG方案的药物，DTG联合TDF前药的抗病毒效果优于传统的EFV方案，TAF组在肾和骨骼安全性上更具优势。一项网状Meta分析结果表明48周病毒抑制率中TAF+FTC+DTG的疗效优，且SUCRA为90.28%[46]。一线ART治疗HIV感染的研究[47]结果显示：EFV、DTG单药的48周病毒抑制率比其他单药结局好（*OR*=1.87，95% *CI*：[1.34，2.64]）。TDF+FTC+DTG在96周病毒抑制率的突出表现，与SINGLE研究（长效注射用帕利哌酮与口服抗精神病药物治疗精神分裂症的随机对照研究）[48]结论存在差异，后者提示TAF与TDF联合DTG的长期疗效差异无统计学意义，这可能与本研究纳入人群的基线特征或合并用药差异有关。

本研究存在以下局限性：（1）纳入研究的方法学质量较低，33.3%的研究并未明确说明随机分配，46%的研究中采用开放性标签，未施行盲法，可能会增加偏倚的风险；（2）对于部分干预措施，纳入的随机对照试验数量有限，这可能会影响研究结果的稳定性和可靠性。针对以上问题，未来可以进一步开展高质量的随机对照试验，基于较高可信度的研究，借助循证方法证实ART药物的疗效，验证本研究结果，临床实践中应严谨看待本研究不同结局药物措施的排序结果。

5 结论

本研究结果显示TAF+FTC+DTG和TDF+FTC+DTG分别在48周和96周的病毒抑制率具有最优疗效，DTG+3TC在96周不良事件发生率最低，体现了其良好的安全性和耐受性。未来仍需高质量、长期随访的随机对照试验进一步验证各方案的优势。

利益冲突声明 本研究不存在研究者、伦理委员会成员、受试者监护人以及与公开研究成果有关的利益冲突。

作者贡献声明 李 盛：质量控制与全文撰写及修改；宁金铃：文献筛选、数据提取与全文撰写；韩 敏、马 艳、王金玉、施文娟、万 红：文献筛选与数据提取；葛 龙：文章修改与质量控制。

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