Effects of Different Integrase Inhibitors on Body Weight in Patients with HIV/AIDS: A Network Meta-Analysis

Ruojing Bai
Capital Medical University Youan Hospital
Shiyun Lv
Capital Medical University Youan Hospital
Hao Wu
Capital Medical University Youan Hospital
Lili Dai (lilydaier@ccmu.edu.cn)
Capital Medical University https://orcid.org/0000-0003-4886-9138

Research article

Keywords: Integrase inhibitors, HIV/AIDS, Body weight, Network meta-analysis

Posted Date: December 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-136545/v1

Abstract

Background: Global antiretroviral therapy has entered the era of integrase strand transfer inhibitor (INSTI). Because INSTIs have the advantages of high antiviral efficacy, rapid virus inhibition, and good tolerance, they have become the first choice in international acquired immunodeficiency syndrome (AIDS) treatment guidelines. However, they may also increase the risk of obesity. There are differences in the effects of different INSTIs on weight gain in Human immunodeficiency virus (HIV) infection / AIDS patients, but there is no evidence-based medical evidence. This study aimed to assess the effect of different INSTIs on body weight in HIV/AIDS patients.

Methods: PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), China Science and Technology Journal Database, and Wanfang databases were searched by computer to screen the relevant literature on INSTI treatment of HIV/AIDS patients, extract the data on weight changes in the literature, and perform network meta-analysis using Stata16.0 software.

Results: Eight articles reported weight changes in HIV/AIDS patients, and weight gain was higher after treatment with dolutegravir (DTG) than with elvitegravir (EVG) in HIV/AIDS patients, and the difference was statistically significant [MD = 1.13, (0.18, 2.07)]. The network meta-analysis's consistency test results showed no overall and local inconsistency, and there was no significant difference in the results of the direct and indirect comparison (P > 0.05). The rank order of probability was DTG (79.2%) > Bictegravir (BIC) (77.9%) > Raltegravir (RAL) (33.2%) > EVG (9.7%), suggesting that DTG may be the INSTI drug that causes the most significant weight gain in HIV/AIDS patients.

Conclusion: According to the literature data analysis, among the existing INSTIs, DTG may be the drug that causes the highest weight gain in HIV/AIDS patients, followed by BIC.

Background

Human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) patients after antiretroviral therapy (ART), the mortality rate decreased significantly[1]. Especially in recent years, integrase inhibitors such as Dolutegravir (DTG), Raltegravir (RAL), Elvitegravir (EVG), and Bictegravir (BIC) are a new class of antiviral drugs. Because of their good efficacy and tolerance[2–4], integrase inhibitors have been recommended by several guidelines[5–8]. However, with the widespread use of integrase strand transfer inhibitor (INSTI), some studies found that patients who used INSTIs gained more weight compared with patients who used conventional antiviral therapy (without INSTIs)[9–10].

In the first two years of ART treatment, patients with HIV/AIDS will have significant weight gain, which has become a recognized problem[11–12]. In the early ART stage, weight gain is an important manifestation of body rehabilitation, indicating the recovery of immunity and improving the survival rate in patients with HIV/AIDS[13–17]. In the past 20 years, the weight of patients has shown a steady increase. A study[18–19] found that more than half of the HIV/AIDS patients who received ART for up to 3 years were overweight or obese, and the potential impact of weight gain was not clear. Obese people have a significantly higher risk of cardiovascular disease, diabetes, or neurocognitive impairment than non-obese people, and obesity may further increase the risk of other non-AIDS-related diseases as HIV/AIDS patients live longer[20–23].

Weight gain differed after treatment with different types of INSTIs.At present, there is no large sample of evidence-based medicine evidence to prove the effectiveness of different INSTIs on the bodyweight of patients with HIV/AIDS. Therefore, in this study, we compared the effects of different INSTIs on body weight in HIV/AIDS patients by network meta-analysis to assess the drugs that cause the most significant weight gain in HIV/AIDS patients.

1 Methods

1.1Meta registration

This meta-analysis is reported according to the general guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.The study protocol has been registered on INPLASY PROTOCOL (registration number INPLASY2020120067).

1.2 Literature Search

PubMed, Embase, CohraneLibrary, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), China Science and Technology Journal Database and Wanfang Databases were searched by computer to screen the relevant literatures on INSTI treatment of HIV/AIDS patients.The search time was from database establishment to October 15, 2020. The searched languages were only Chinese and English. Search terms: "AIDS", "HIV", "Acquired Immunodeficiency Syndrome", "weight", "RAL", "EVG", "DTG", "BIC", "RAL", "DTG", "EVG", "BIC", "Integrase strand transfer inhibitor", and the search formula is:((((AIDS) OR (HIV)) OR (Acquired Immunodeficiency Syndrome)) AND (weight)) AND ((((((((((RAL) OR (EVG)) OR (DTG)) OR (BIC)) OR (RAL)) OR (DTG)) OR (EVG)) OR (BIC)) OR (Integrase strand transfer inhibitor)).

1.3 Inclusion And Exclusion Criteria

Inclusion criteria:(1) the subjects included in the literature were HIV/AIDS patients with a definite diagnosis; (2) the interventions in the literature were various types of INSTIs; (3) the outcome measure in the literature was weight change before and after treatment; (4) the result data in the literature were complete.

Exclusion criteria:(1) The results are not completely statistically analyzed or the relevant data are insufficient; (2) Repeated publication of the literature; (3) The number of cases included in the observation group or the control group of the study is too small; (4) Conference, meta-analysis and review of the literature.

1.4 Literature screening and data extraction

The retrieved literature was initially screened by two investigators independently according to the inclusion and exclusion criteria and then cross-checked. The controversial literature was evaluated by the third party and unified by discussion. Two investigators extracted the relevant information of the included literature, including first author, publication year, publication country, sample size, age, gender, and weight change.

1.5 Literature quality evaluation

Since the included studies were cohort studies or randomized controlled studies, the literature's quality was evaluated using the Newcastle-Ottawa scale (NOS) scale or the Jadad scoring scale.

1.6 Statistical Methods

The data were analyzed using STATA version 16.0 software. Measurement data were expressed as weighted mean difference (MD), and interval estimation was performed using a 95% confidence interval (CI) as an indicator of effect size. When the data extracted from the literature are brought into the stata16.0 version of the software for calculation, the node-splitting model in the software is used to compare the results of direct comparison with those of indirect comparison, to observe whether the two results are consistent, and then to make clear the consistency test results. If there was no statistical difference ($P > 0.05$), the consistent model was used for network meta-analysis of various drugs; if there was the statistical difference ($P < 0.05$), the source of non-consistency was analyzed in detail. After comparing multiple interventions, rank probability ranking plots were used to rank the interventions and assess the drug that caused the most significant weight gain.

2. Results

2.1 process and results of literature retrieval.

Four hundred ninety-seven related original articles were found in this network Meta-analysis, including 493 in English and 4 in Chinese, involving four intervention measures: DTG, RAL, EVG, and BIC. By carefully reading the titles and abstracts, screening the literature according to the inclusion and exclusion criteria, 65 articles were obtained and then excluded again by reading the full text. Finally, this study included eight articles[10,24–30] (Fig. 1).

2.2 Basic characteristics and quality evaluation of the included literature

Among the eight included literature, there were 11,339 patients. The basic characteristics and quality evaluation of the included studies are shown in Table 1. The quality evaluation of the included studies showed that the overall quality of the literature was high.

Table 1
Basic characteristics and quality evaluation of the included studies

Author	Year	Country	Type of Study	Sex(M/F)	Ages	Sample Sizes	Interventions	NOS/Jadad Scores
Leonardo Calza[24]	2019	Italy	Cohort study	138/58	43.1 ± 15.2	196	RAL	6
				115/59	41.6 ± 12.8	174	DTG	
				109/49	42.5 ± 13.6	158	EVG	
Peter F[25]	2020	USA	Cohort study	917/164	44(33–52)	1081	RAL	7
				2058/257	34(27–45)	2315	EVG	
				1044/166	35(28–48)	1210	DTG	
Kassem Bourgi[26]	2019	USA	Cohort study	NA	NA	63	RAL	5
				NA	NA	153	EVG	
				NA	NA	135	DTG	
Kassem Bourgi[27]	2020	USA	Cohort study	1016/176	NA	1192	RAL	7
				795/131	NA	926	DTG	
				1842/226	NA	2068	EVG	
Sax PE[10]	2019	USA	RCT	565/74	37 ± 11.9	639	DTG	4
				434/67	38 ± 9.5	501	BIC	
				567/62	34 ± 10.8	629	EVG	
David A Wohl[28]	2019	USA	RCT	282/33	35(26–40)	315	DTG	4
				285/29	31(25–41)	314	BIC	
Stellbrink[29]	2019	Germany	RCT	280/40	33(27–46)	320	BIC	6
				288/37	34(27–46)	325	DTG	

NA: Not available; F: Female; M: Male; RCT: Randomized controlled trial

Author	Year	Country	Type of Study	Sex(M/F)	Ages	Sample Sizes	Interventions	NOS/Jadad Scores
Lake[30]	2020	USA	Cohort study	NA	NA	198	DTG	5
				NA	NA	204	EVG	
				NA	NA	289	RAL	
NA: Not available; F: Female; M: Male; RCT: Randomized controlled trial								

2.3 Evidence Network

Relationships among all intervention methods were formed based on direct comparison data. Each vertex of the relationship diagram represents different intervention methods, respectively. The size of the vertex represents the sample size included in each intervention method. The line between the vertices represents the direct comparison between the two intervention methods. The thickness of the line is directly proportional to the number of studies on each pair of intervention methods. There is direct or indirect evidence between different intervention methods, with the basic conditions for performing network meta-analysis (Fig. 2).

2.4 Network Meta-analysis

Eight articles reported weight changes in HIV/AIDS patients, and after DTG treatment, weight gain was higher than EVG, and the difference was statistically significant [MD = 1.13, (0.18, 2.07)]. There were no significant differences in BIC vs DTG, BIC vs EVG, BIC vs RAL, DTG vs RAL, and EVG vs RAL.

Table 2 results of a network Meta-analysis of weight gain in patients with HIV/AIDS (MD,95%CI)

Table 2
results of a network Meta-analysis of weight gain in patients with HIV/AIDS (MD,95%CI)

BIC			
0.06 (-1.15,1.27)	DTG		
1.19 (-0.22,2.60)	1.13 (0.18,2.07)	EVG	
0.80 (-0.70,2.29)	0.73 (-0.22,1.69)	-0.39 (-1.42,0.63)	RAL

2.5 Ranking of Probability for Weight Gain for Each Drug

The rank order of probability was DTG (79.2%) > BIC (77.9%) > RAL (33.2%) > EVG (9.7%), suggesting that DTG may be the drug that causes the most significant weight gain in HIV/AIDS patients (Fig. 3).

2.6 Consistency Test

The whole study's inconsistency test results showed no significant difference between direct comparison and indirect comparison (P > 0.05). Therefore, there was no inconsistency between direct comparison and indirect comparison. The results of node analysis showed that there was no significant difference in direct and indirect comparison between BIC vs DTG, BIC vs EVG, DTG vs EVG, DTG vs RAL, and DTG vs RAL (P > 0.05), indicating that there was no local inconsistency (Table 3).

Table 3
Node analysis of direct and indirect comparisons among interventions

Category	Direct		Indirect		Difference		P
	Coef	Std.Err	Coef	Std.Err	Coef	Std.Err	
BIC vs DTG	-0.162	0.668	1.105	2.301	-1.267	2.396	0.597
BIC vs EVG	-0.760	1.159	-1.504	0.985	0.744	1.521	0.625
DTG vs EVG	-1.160	0.527	-0.752	1.829	-0.408	1.904	0.831
DTG vs RAL	-0.795	0.521	0.472	2.338	-1.267	2.396	0.597
EVG vs RAL	0.463	0.586	-0.113	1.575	0.576	1.680	0.732
Coef: coefficient;Std.Err: Standard Error							

3 Discussion

INSTI is a class of drugs with high antiviral activity. In some studies, it was found that on the 10th day after treatment, HIV RNA levels in RAL, EVG, DTG and BIC groups could be reduced by 2.16 $\log_{10}$ copies/ml[31], 1.99 $\log_{10}$ copies/ml[32], 2.46 $\log_{10}$ copies/ml[33] and 2.43 $\log_{10}$ copies/ml[34], respectively. However, after protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment, the maximum amplitude of HIV RNA decrease was below 2 (1.29 ~ 1.99) $\log_{10}$ copies/ml from 7 to 14 days[35–38].

In many clinical trials of RAL, EVG, and DTG compared with NNRTI and PI drugs, INSTI showed good safety and tolerability, significantly reduced central nervous system adverse reactions compared with Efavirenz (EFV), and also significantly superior to PI drugs in terms of blood lipids and gastrointestinal adverse reactions[39–41]. The most common adverse reactions of INSTIs are nausea, vomiting, diarrhea, headache, and fatigue, and the severity of adverse reactions is only mild to moderate. Since the first INSTI was applied in 2007, its overall acquired drug resistance rate is still low. The drug resistance rates of RAL, EVG, and DTG are 3.9%, 1.2%, and 0.1%, respectively[42]. In comparison, about 10–17% of treatment-naive HIV-infected individuals in high-income countries are resistant to NNRTIs, PI resistance is relatively rare, INSTI resistance transmission is even rarer, and DTG and BIC have a relatively higher resistance barrier[43].

Given the high efficiency, safety, tolerability, and low drug resistance of INSTIs, ART has entered the era of INSTIs.However, with the widespread use of integrase, some studies have found that the application of integrase is associated with significant weight gain in infected individuals and even overweight in infected individuals. From the results of the probability ranking of the interventions in this study, it can be found that DTG is the drug that causes the most significant weight gain of patients among all INSTIs.The mechanisms by which different INSTIs contribute to weight gain are ambiguous and may be associated with multiple factors. An in vitro study

reported that DTG in INSTI could inhibit the melanocortin four receptors (MC4R)[44].MC4R plays a role in human energy homeostasis and correlates with human body weight. When the investigators knocked out the mice's MC4R gene, the mice showed severe obesity[45]. Therefore, after MC4R inhibition by DTG, the patient's body weight increased relatively more easily.Some scholars have pointed out that the difference in weight gain may be related to the inconsistent effect of different INSTIs on adipocytes. A study[46] found that the drug concentrations of different antiretroviral drugs in adipocytes are different, with higher DTG and EVG. An in vitro study[47] has demonstrated that EVG impairs adipocytes' metabolism, but RAL does not appear to damage adipocytes. Another hypothesis that may contribute to weight gain is that INSTIs affect the gut microbiota in HIV/AIDS patients[48]. Studies by ElKamariV et al. [49] found that fatty acid-binding protein, as a marker of intestinal integrity, its level can be used as an independent predictor of weight gain and visceral fat gain in HIV/AIDS patients. Thus, the mechanism by which INSTIs cause weight gain in HIV/AIDS patients is not fully explained by a factor or mechanism.

An important reason for weight gain has attracted much attention because weight gain will increase the risk of non-AIDS-related diseases such as cardiovascular and cerebrovascular diseases in infected individuals. However, the risk of metabolic or cardiovascular diseases in HIV/AIDS patients cannot be completely and accurately predicted by the degree of obesity alone, which is due to the area of human fat distribution. Visceral fat or vascular content is bound to increase the risk of visceral or vascular diseases. Since the original literature included in this study did not analyze the differences between fat in peripheral or central regions of the body in HIV/AIDS patients, we could not assess the increase of fat in different body regions in HIV/AIDS patients INSTI. Besides, whether some important metabolic parameters are correspondingly altered has not been effectively confirmed. It is expected that there will be subsequent studies on fat gain and metabolic parameters in different regions of the body in HIV/AIDS patients, and such results may be better able to guide the long-term health of HIV/AIDS patients.

The conclusions drawn from this study have certain reference value. However, since this original literature's quality was not as good as that of the randomized controlled trial in the included literature, the study subjects in the literature may have differences in basal body mass index, CD4 + T cell count, and patients' dietary habits. The correlation between these factors and weight change could not be excluded. Therefore, the conclusions drawn from this literature's data were not as strong as those of the randomized controlled trial. Besides, this study's conclusions are based on network Meta, and the strength of evidence is also weaker than the results of a direct comparison. Therefore, the interpretation of this study's conclusions should be cautious, and subsequent randomized controlled trials with rigorous design and large sample size are still needed to confirm further.

4. Conclusion

Based on data from the available literature, it is confirmed that DTG increases body weight most significantly in HIV/AIDS patients, while BIC is second only to DTG. However, there are still unresolved issues. It is unclear whether INSTI-based regimens cause lipohypertrophy (particularly an increase in visceral fat) or whether they increase the risk of cardiometabolic complications. As we continue to explore the road to ART, a more detailed description of these relevant studies that do not solve the problem has behaved crucially.

Abbreviations

INSTI: integrase strand transfer inhibitor; HIV: Human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; CNKI: China National Knowledge Infrastructure; CBM: Chinese Biomedical Literature Database; DTG: dolutegravir; EVG: elvitegravir; BIC: Bictegravir; RAL: Raltegravir; ART: antiretroviral therapy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MD: mean difference; 95%CI: Confidence interval; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; EFV: Efavirenz; MC4R: melanocortin four receptors; NA: Not available; F: Female; M: Male; RCT: Randomized controlled trial; Coef: coefficient; Std.Err: Standard Error

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Funding Sources

This work was supported by the National 13th Five-Year Grand Program on Key Infectious Disease Control (Grant number:2018ZX10721102–003-003、2018ZX10302-102). LD is the funder, who revised the manuscript for important intellectual content.

Author Contribution

RB,SL conceived, designed, and performed the analysis. LD verified the analytical methods. RB,SL wrote the paper and revised the manuscript for important intellectual content. HW revised the manuscript for important intellectual content. All authors discussed the results and contributed to the final manuscript.

Acknowledgements

Thanks to all authors for their contributions to this manuscript.

Availability of data and materials

All the data and materials are available from Pubmed, Cochrane Library, MEDLINE/EMBASE and Web of Science.

References

1. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. Curr Opin Infect Dis. 2020 Feb;33(1):10–9.
2. Iwamoto M, Wenning LA, Petry AS, et al. Safety, tolerability, and pharmacokinetics of RAL after single and multiple doses in healthy subjects. Clin Pharmacol Ther. 2008 Feb;83(2):293–9.

3. Mondi A, Cozzi-Lepri A, Tavelli A, et al. Effectiveness of DTG-based regimens as either first-line or switch antiretroviral therapy: data from the Icona cohort. J Int AIDS Soc. 2019 Jan;22(1):e25227.
4. McComsey GA, Moser C, Currier J, et al. Body Composition Changes After Initiation of RAL or Protease Inhibitors: ACTG A5260s. Clin Infect Dis. 2016 Apr 1;62(7):853 – 62.
5. European AIDS. Clinical Society.European AIDS Clinical Society (EACS) guidelines. London: EACS; 2018. 9.1.
6. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and postexposure prophylaxis and recommendations on early infant diagnosis of HIV. Geneva: WHO; 2018.
7. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2018 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2018 Jul;24(4):379–96. 320(.
8. British HIV, Association. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy (interim update). London: BHIVA; 2016.
9. Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc. 2020 Apr;23(4):e25484.
10. Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2020 Sep 12;71(6):1379–1389.
11. Sattler FR, He J, Letendre S, et al. Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. J Acquir Immune Defic Syndr. 2015 Mar 1;68(3):281-8.
12. Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. J Antimicrob Chemother. 2018 Aug 1;73(8):2177–2185.
13. Yuh B, Tate J, Butt AA, et al. Weight change after antiretroviral therapy and mortality. Clin Infect Dis. 2015 Jun 15;60(12):1852–9.
14. Paton NI, Sangeetha S, Earnest A, et al. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Med. 2006 Jul;7(5):323–30.
15. Madec Y, Szumilin E, Genevier C, et al. Weight gain at 3 months of antiretroviral therapy is strongly associated with survival: evidence from two developing countries. AIDS. 2009 Apr 27;23(7):853–61.
16. Koethe JR, Limbada MI, Giganti MJ, et al. Early immunologic response and subsequent survival among malnourished adults receiving antiretroviral therapy in Urban Zambia. AIDS. 2010 Aug;24(13):2117–21. 24(.
17. Koethe JR, Lukusa A, Giganti MJ, et al. Association between weight gain and clinical outcomes among malnourished adults initiating antiretroviral therapy in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2010 Apr 1;53(4):507 – 13.
18. Koethe JR, Jenkins CA, Lau B, et al. Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada. AIDS Res Hum Retroviruses. 2016 Jan;32(1):50–8.
19. Crum-Cianflone N, Roediger MP, Eberly L, et al. Increasing rates of obesity among HIV-infected persons during the HIV epidemic. PLoS One. 2010 Apr 9;5(4):e10106.
20. Lakey W, Yang LY, Yancy W, et al. Short communication: from wasting to obesity: initial antiretroviral therapy and weight gain in HIV-infected persons. AIDS Res Hum Retroviruses. 2013 Mar;29(3):435–40.

21. Koethe JR, Jenkins CA, Lau B, et al. Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada. AIDS Res Hum Retroviruses. 2016 Jan;32(1):50–8.
22. Herrin M, Tate JP, Akgün KM, et al. Weight Gain and Incident Diabetes Among HIV-Infected Veterans Initiating Antiretroviral Therapy Compared With Uninfected Individuals. J Acquir Immune Defic Syndr. 2016 Oct 1;73(2):228 – 36.
23. Sattler FR, He J, Letendre S, et al. Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. J Acquir Immune Defic Syndr. 2015 Mar 1;68(3):281-8.
24. Calza L, Colangeli V, Borderi M, et al. Weight gain in antiretroviral therapy-naive HIV-1-infected patients starting a regimen including an integrase strand transfer inhibitor or darunavir/ritonavir. Infection. 2020;48(2):213–21.
25. Rebeiro PF, Jenkins CA, Bian A, et al. Risk of Incident Diabetes Mellitus, Weight Gain, and their Relationships with Integrase Inhibitor-based Initial Antiretroviral Therapy Among Persons with HIV in the US and Canada [published online ahead of print, 2020 Sep 16]. Clin Infect Dis. 2020;ciaa1403.
26. Bourgi K, Rebeiro PF, Turner M, et al. Greater Weight Gain in Treatment-naive Persons Starting DTG-based Antiretroviral Therapy. Clin Infect Dis. 2020;70(7):1267–74.
27. Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc. 2020;23(4):e25484.
28. Wohl DA, Yazdanpanah Y, Baumgarten A, et al. BIC combined with emtricitabine and tenofovir alafenamide versus DTG, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2019;6(6):e355–63.
29. Stellbrink HJ, Arribas JR, Stephens JL, et al. Co-formulated BIC, emtricitabine, and tenofovir alafenamide versus DTG with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV. 2019;6(6):e364–72.
30. Lake JE, Wu K, Bares SH, et al. Risk Factors for Weight Gain Following Switch to Integrase Inhibitor-Based Antiretroviral Therapy [published online ahead of print, 2020 Feb 26]. Clin Infect Dis. 2020;ciaa177.
31. Norwood J, Turner M, Bofill C, et al. Brief Report: Weight Gain in Persons With HIV Switched From Efavirenz-Based to Integrase Strand Transfer Inhibitor-Based Regimens. J Acquir Immune Defic Syndr. 2017;76(5):527–31.
32. Markowitz M, Morales-Ramirez JO, Nguyen BY,et al.Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518,a novel inhibitor of HIV-1 integrase,dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals[J].J Acquir Immune Defic Syndr,2006,43(5):509–515.
33. De Jesus E, Berger D,Markowitz M,et al. Antiviral activity,pharmacokinetics,and dose response of the HIV-1 integrase inhibitor GS-9137(JTK-303)in treatment-naive and treatmentexperienced patients[J]. J Acquir Immune Defic Syndr. 2006;43(1):1–5.
34. Min S, Sloan L, De Jesus E,et al.Antiviral activity,safety,and pharmacokinetics/ pharmacodynamics of DTG as 10-day monotherapy in HIV-1-infected adults[J].AIDS,2011,25(14):1737–1745.
35. Gallant JE, Thompson M, De Jesus E,et al.Antiviral activity,safety,and pharmacokinetics of BIC as 10-Day monotherapy in HIV-1-infected adults[J].J Acquir Immune Defic Syndr,201775(1):61–66.

36. Gruzdev B,Rakhmanova A,Doubovskaya E,et al.A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naive,HIV-1 infected subjects[J].AIDS,2003,17(17):2487–2494.
37. Goebel F, Yakovlev A, Pozniak AL,et al.Short-term antiviral activity of TMC278–a novel NNRTI–in treatment-naive HIV-1-infected subjects[J].AIDS, 2006,20(13):1721–1726.
38. Murphy RL, Brun S, Hicks C,et al.ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection:48-week results[J].AIDS,200115(1):F1-F9.
39. Arastéh K,Clumeck N,Pozniak A,et al.TMC114/ritonavir substitution for protease inhibitor(s)in a non-suppressive antiretroviral regimen:a 14-day proof-of-principle trial[J].AIDS,2005,19(9):943–947.
40. Lennox JL, De Jesus E, Lazzarin A,et al.Safety and efficacy of RAL-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection:a multicentre,double-blind randomised controlled trial[J].Lancet,2009, 374(9692):796–806.
41. De Jesus E, Rockstroh JK,Henry K,et al. Co-formulated EVG, cobicistat, emtricitabine,and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection:a randomised,double-blind,phase 3,noninferiority trial[J]. Lancet. 2012;379(9835):2429–38.
42. Walmsley SL. Antela A,Clumeck N,et al.DTG plus abacavir-lamivudine for the treatment of HIV-1 infection[J]. NEngl J Med. 2013;369(19):1807–18.
43. You J, Wang H, Huang X,et al.Therapy-emergent drug resistance to integrase strand transfer inhibitors in HIV-1 patients:a subgroup meta-analysis of clinical trials[J].PLo S One,2016,11(8):e0160087.
44. European Medicines Agency Assessment Report of Dolutegravir (Tivicay). Available at . Accessed Dec 9, 2019.
45. Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell. 1997;88(1):131–41.
46. Macallan DC, Noble C, Baldwin C, et al. Energy expenditure and wasting in human immunodeficiency virus infection. N Engl J Med. 1995;333(2):83–8.
47. Couturier J, Winchester LC, Suliburk JW, et al. Adipocytes impair efficacy of antiretroviral therapy. Antiviral Res. 2018;154:140–8.
48. Moure R, Domingo P, Gallego-Escuredo JM, et al. Impact of EVG on human adipocytes: Alterations in differentiation, gene expression and release of adipokines and cytokines. Antiviral Res. 2016;132:59–65.
49. El Kamari V, Moser C, Hileman CO, et al. Lower Pretreatment Gut Integrity Is Independently Associated With Fat Gain on Antiretroviral Therapy. Clin Infect Dis. 2019;68(8):1394–401.

Figures

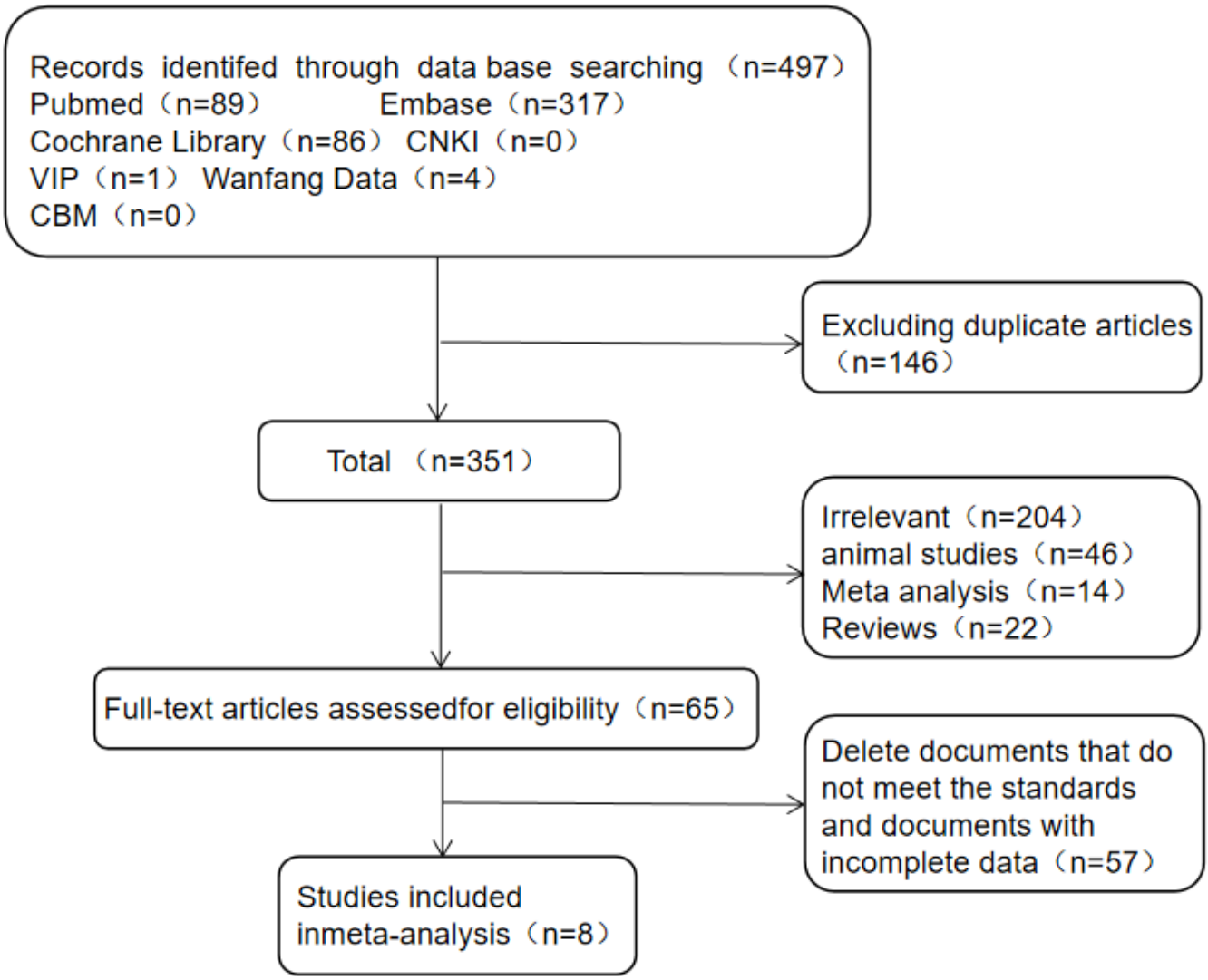

Figure 1

Literature screening flow chart.

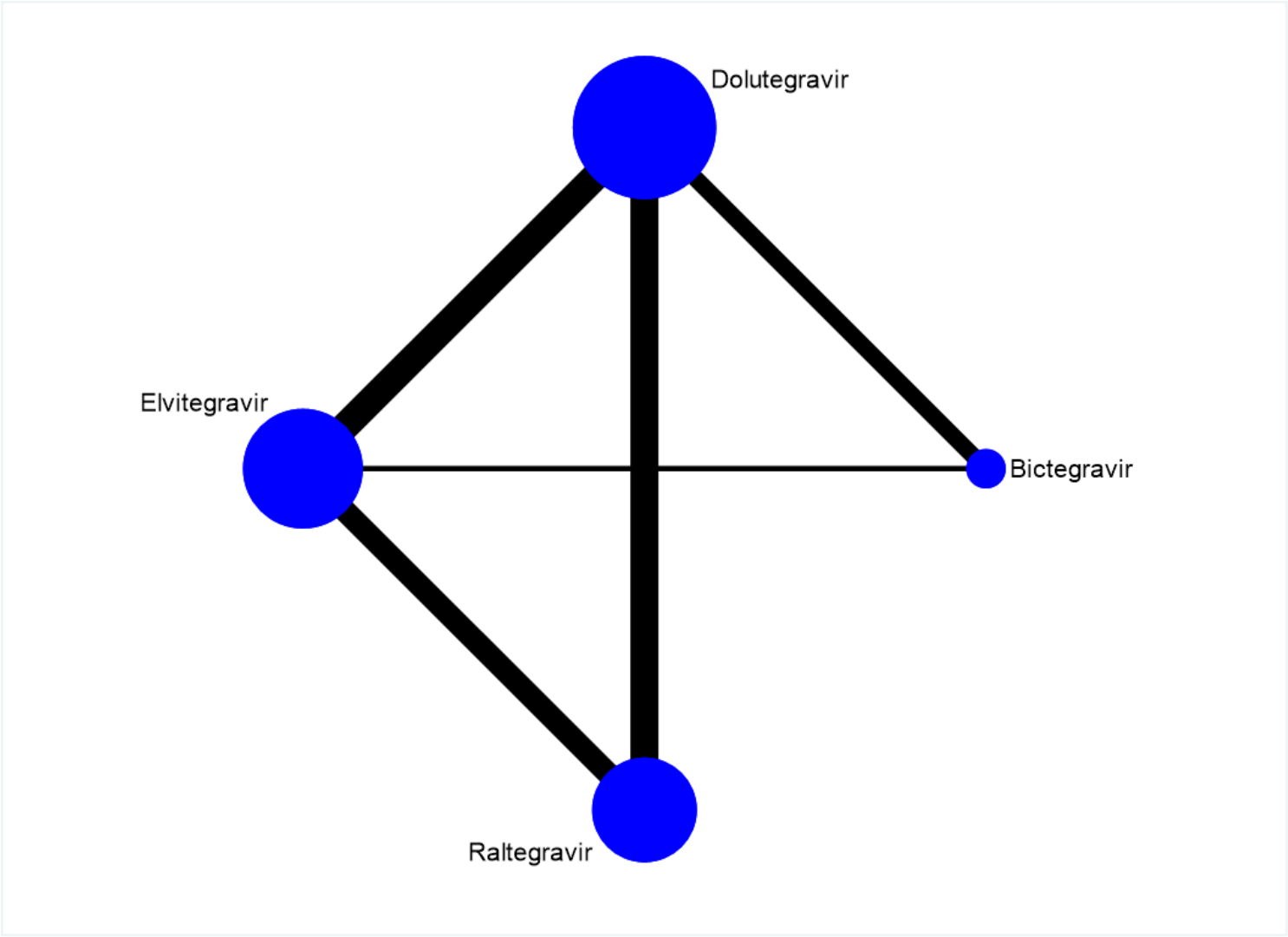

Figure 2

Network evidence diagram.

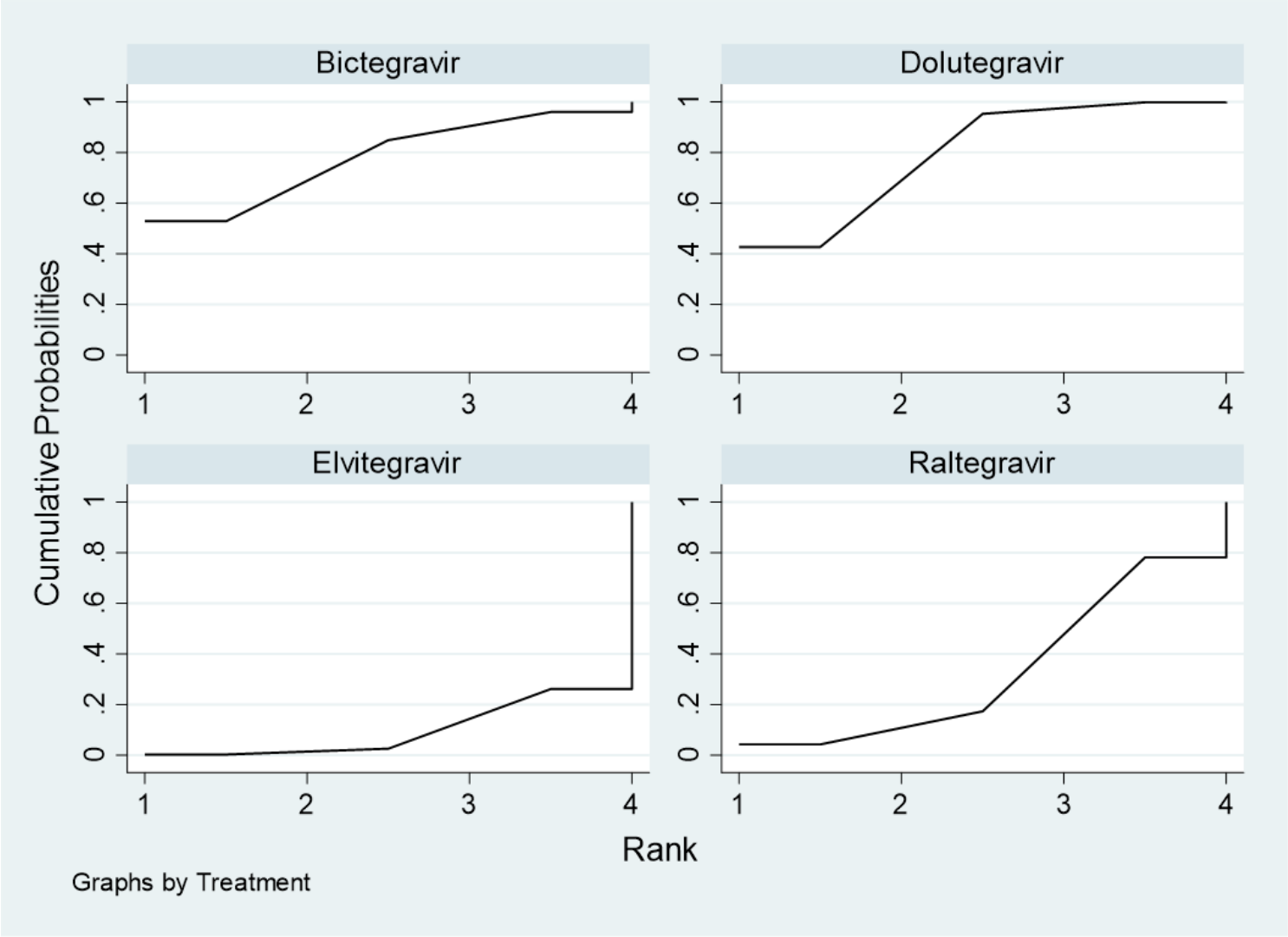

Figure 3

Probability ranking of each drug to increase body weight in HIV/AIDS patients (SUCRA)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc