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Effects of ART in HIV Infected Population on Body Habitus Change: A Multilevel Meta-analysis

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Effects of ART on HIV Infected Population on Body Habitus Change: A Multilevel Meta-analysis

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ABSTRACT

Importance: Different ART treatments to HIV patients has been shown to be effective in improving a variety of disease outcomes, including CD-4 cell count improvements and viral suppressions. In addition to these improvements, investigators are also interested to evaluate the association between ART treatments and the body habitus changes of the HIV patients. It is unclear that which body habitus change outcomes are more greatly associated with what type of ART treatments and how those effects could vary depending on context and sample characteristics.

Objective: To obtain overall effect sizes for the body habitus change outcome variables (weight, body mass index, trunk fat, limb fat and lipid parameters) and explain the variability among different ART treatments/interventions (NRTI, NNRTI, PI and combination HAART medicines) considering all treatments clustered within the current literatures using multilevel approach for meta-analysis.

Data Sources: Five electronic databases (PubMed, Scopus, CINAHL, PYCHINFO and Cochrane Controlled Trials register) were searched starting on July 6, 2015 using a comprehensive Boolean Search Strategy.

Study Selection: Studies were included if pre-and post- intervention measurements of body habitus changes were reported and NRTI, NNRTI, PI, and combination HAART medicines LPV/r vs ABC/3TC + LPV/r; LPV/r +ZDV/3TC vs LPV/r NVP; PI compared alone or, in combination with other ARTs and NNRTI compared alone or, in combination with other ARTs were used as treatments to HIV patients. Data from 20 studies (N = 376) were included.

Data Extraction and Synthesis: Two independent researchers identified studies that met the inclusion criteria and coded methodological, participant, and treatment characteristics using a pilot tested structured coding form. Inter-rater agreement was evaluated using Cohen's kappa coefficient statistic and effect size was calculated as standardized mean difference as all outcome variables were continuous.

Main Outcomes and Measures: Weighted mean effect size under random-effects assumption were obtained and modeled after pooling the individual standardized mean differences for each study on the five-body habitus change outcomes.

Results: There were significant beneficial effects of the LPV/r combination category on weight and BMI [d+ = 0.44, 95% CI (0.18 to 0.71)]; [d+ = 0.94, 95% CI (0.53 to 1.3)] respectively. PI combination category has beneficial effect [d+ = 0.44, 95% CI (0.2601 to 0.6311)] for limb fat. Level of HDL significantly increased in all three combination categories but more in favor of NNRTI combination category with large impact [d+ = 0.85, 95% CI (0.54 to 1.15)], p-value of <0.0001. Multilevel analysis results inferred that estimates for HDL were statistically significantly different in three combination HAART treatment categories (i.e., LPV/r, PI and NNRTI combined HAART categories) with p= <0.0001, p=0.01 and p= <0.0001 respectively. Estimates for LDL were significantly different in NNRTI alone, LPV/r and NNRTI combined HAART categories. For trunk and limb-fat, variations were statistically significantly different between PI alone and NNRTI combined HAART, with corresponding p=<0.0001. Moderation analysis indicated that, level of LDL decreases by 0.004 units when length of intervention or, week increases. Limb fat increases by 0.06 units as more recent the publication is. HDL, LDL and TG decreases by 0.06, 0.005 and 0.07 units due to advancement of research.

Level of HDL and LDL decreases 0.006 and 0.01 units as number of female patients increases in the sample, meaning that, chances of increased HDL and LDL level is less in large female patients. Level of blood cholesterol and TG decreases 0.17 and 0.07 units due to the aging process. Proportion of white population has significant moderation effect on trunk fat, limb fat, cholesterol with no significant effects on weight, BMI, LDL, HDL and TG and methodological quality modified only limb fat. Trunk fat, limb fat and cholesterol increases 0.64, 0.73 and 0.50 units when proportion of white population increases. Methodological quality (MQ) score has moderated limb fat by 0.18 units indicating that due to good quality research/ high quality score, limb fat is increasing for the betterment of body balance.

Conclusions and Relevance: LPV/r combined HAART is more effective with moderate increase of weight and BMI. PI combined HAART has significant impact on limb fat improvement which could be used to maintain body proportion in HIV patients as limb fat loss is a major concern. NNRTI combined treatment category showed large impact on HDL which might be prescribed as HDL reduces cardiovascular risk.

INTRODUCTION

Global Facts on HIV

Human Immunodeficiency Virus (HIV) infection is a slow progressive infectious health condition that weakens human immune system. Approximately 36.9 million people are now living with HIV worldwide. The Centers for Disease Control and Prevention (CDC) report stated that 1.2 million people are living with HIV in the United States. Chances of new HIV infection remains static but the number of people living with HIV has increased over the past decades since the epidemic began. The majority of new HIV infected populations are men having sex with men (MSM), accounting for 78% in 2010. The prevalence of new HIV infections among women was reduced 21% from 2008 to 2010. Racial context reflects that HIV is more likely within African Americans, who made up 44% of new HIV infections in 2010 (1). HIV infection is not curable; however, effective treatment with HIV-medications can suppress viral replication and increase CD4 cell counts, which reduces HIV-associated mortality, morbidity and hospitalizations with subsequent improvements in health quality.

FDA approved HIV-medicines with their mode of action

UNAIDS 2014 report regarding the accessibility of antiretroviral therapy (ART) highlighted that 76% of HIV infected populations undergo ART globally to reduce chances of spreading HIV to their sexual partners (2). The Food and Drug Administration (FDA) has classified ART into eight categories, including nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), combination forms of ART, fusion inhibitors, pharmacokinetic enhancers, entry inhibitors, and integrase inhibitors with their subclasses

(3). For this study, we considered only NRTIs, NNRTIs, PIs and combination of HAART following FDA provided classifications those are made up of two or more medicines from one or, more HIV medicine classes such as two NRTIs, three NRTIs, two NRTIs plus one NNRTI, two NNRTIs plus one PI, NRTI plus NNRTI plus PI and Ritonavir boosted Lopinavir (LPV/r) considering widely prescribed HIV medicines by the practitioners to treat HIV patients.

HIV-medicines vary in their mode of action to minimize chances of viral replication. Nucleoside reverse transcriptase inhibitor (NRTI) inhibits viral reverse transcriptase by targeting RNA dependent DNA polymerase chains. Non-nucleoside reverse transcriptase inhibitor (NNRTI) inhibits the reverse transcriptase without intracellular phosphorylation. In addition, protease inhibitor (PI) binds with proteins, inhibits structural protein formation, and prevents the spread of viral infection (4). Healthcare providers use combination of any three types of ART or, HAART as standard of care treatment to combat against HIV-infection (5 -6). There is no known explanation for HAART's mode of action.

Immunological Response

Immunologic and virologic responses may vary from one study to another due to the selection of different ARTs by the healthcare providers and there is a lack of written protocol/direction selecting medicines according to stages of HIV. One study examined adult antiretroviral naïve HIV patients who received HAART containing protease inhibitors with a median follow up of 18 months. Researchers did not find significant viral and immunological cell differences before and after HAART intervention (7). A

multicenter randomized clinical trial compared two subclasses of NRTIs along with NNRTI (emtricitabine plus didanosine and efavirenz vs. stavudine plus didanosine and efavirenz). At week 24, mean CD-4 cell count increased 156 cells/microliters for the emtricitabine group vs 119 cells/microliter for the stavudine group (39). To determine the strength of the association between the degree of the effects of HAART, one study conducted a meta regression analysis to assess changes in CD4 cells, viral RNA and progression of AIDS as outcome measures. The result explained no significant changes for CD-cell counts and viral load considering 24, 48 and 96 weeks as treatment time points along with no significant relationship between CD4 cell count changes and progression to AIDS or death (61). Above scientific evidence provided information on immunologic response at varying time points due to different antiviral treatments. Further research is needed addressing time frame for each antiviral treatment.

Defining Body Habitus Change

The benefits of antiretroviral therapy require life-long commitment, which causes varying degrees of bodily changes having both positive and negative effects. In 1999, researchers used the term “Body Habitus Abnormalities” to assess anthropometric and metabolic changes in HIV patients due to HAART in a Multicenter AIDS Cohort Study, where they collected data based on the Third National Health and Nutritional Examination Survey and reported on body habitus alteration/change (8). Metabolic and anthropometric parameters usually started to change abnormally within 2 years of HAART introduction, causing imbalance in lipid profile and site-specific alteration in body fat, resulting in subcutaneous fat loss from limbs, buttocks, face and fat deposition

in the intra-abdominal region or trunk with a clinical evidence in 20-35% of HIV-infected patients (6, 9-12). This imbalance of body constituents is associated with metabolic instability leading to hyperlipidemia and truncal or central fat accumulation that causes central obesity (13-14). Recent studies provided evidence that, obesity is progressing as an epidemic in HIV infected patients (62-64) and increasing more rapidly due to the use of new forms of antiviral therapies (65). Patients living with HIV infection along with increased body mass index due to obesity are more vulnerable towards health-related risks and may cause rapid abnormal change in the body habitus due to having two disease conditions together.

Research teams used models to visualize the actual mechanism of body fat/body habitus changes. Pro-inflammatory cytokines such as tumor necrosis factor alfa acts as a mediator in the pathogenesis of body fat changes caused by viral infection and the development of a persistent inflammatory state (15). In addition, the action of viral proteins with paracrine and endocrine actions on adipose tissue alters adipose differentiation and function. As adipose tissue receives hormonal and neuronal signals, subcutaneous and visceral parts of human body differ functionally, metabolically and genetically due to the adipocyte dysfunction which is responsible for developing chronic conditions and severity in body habitus alterations (4, 15-16).

Body fat changes due to HIV infection are also associated with length of intervention period considering different antiviral treatments as interventions, type of treatments as physicians prescribe different HIV medicines such as ART alone or in combination, and patient demographic characteristics such as age, sex and ethnicity. One prospective cohort study aimed to assess body fat changes in anti-retroviral naïve HIV-

infected adults who received HAART including two NRTIs plus at least one PI with 18 months follow up period and found that the chances of central obesity is 7.7 per 100 patients in one year. (7). To measure limb fat, trunk fat and metabolic features, a multicenter randomized study considered combination HIV medicines comparing ritonavir-boosted lopinavir plus zidovudine/lamivudine (ZDV/3TC/LPV/r) with ritonavir-boosted lopinavir plus nevirapine (NVP/LPV/r) in HIV treatment naïve patients. Data analysis explain that, trunk fat increased in both treatment groups but limb fat increased in ritonavir-boosted lopinavir plus nevirapin (NVP/LPV/r) group and decreased in the other group (50). An observational study included 74 HIV-infected patients with a follow-up period of 24 months, where subjects divided into NNRTI and PI treatment groups by targeting weight, BMI and percentages of body fat to understand degrees of body habitus changes. Results from the study reveal that body weight and BMI increased significantly in PI group at 12 months with no change in NNRTI group. Total body fat decreased more than 20% comprising 16% patients on PI treatment group and 18% on NNRTI group concluding that body fat changes were minor and more common on PI (17). A prospective observational research study assessed ethnicity and gender differences in HIV patients receiving antiviral therapy with imbalance in limb and trunk fat or, lipodystrophy. Results section suggested that, white HIV male patient loss peripheral fat and gained central or, trunk fat, on the other hand, black females were more prone to lipodystrophy. Sex comparison showed that, female HIV patients gained central fat and males reported loss of limb fat (66). Researchers investigated association in body habitus changes with treatment length. Gender and ethnic difference only point out body fat constituents but not metabolic factors and anthropometrics targeting body mass index

and weight in HIV patients. In addition, to our knowledge no study considered individual age as risk factor which needs to be addressed very carefully as aging is an important natural process which can lead to fatal health conditions.

Assessment Techniques

Dual-energy x-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (USG) are different techniques used to measure body fat in general. DEXA and CT scans are the gold standard methods to measure body fat (18). DEXA imaging is feasible and used in HIV clinics for the assessment of total fat, trunk fat and limb fat in kilograms, while CT scan method used to evaluate visceral, subcutaneous and total abdominal fat in square centimeters. Height, weight, waist circumference and body mass index may provide additional information as recent observational studies documented on nutritional alteration due to ART in HIV patients resulting weight gain which might act as stimulating factor enhancing cardiovascular risk (19-20).

Significance/Rationale

The current evidence points out that investigators are not only focusing on CD-4 cell count improvements and viral suppressions, but also trying to minimize abnormal body composition changes such as changes in weight, body mass index, body fat and lipid profile those can increase the risk of cardiovascular diseases due to different ART use. There are controversies about the clinical practice associated with HIV-medicine selection among health care providers along with the prevalence of body habitus abnormalities. Facts related to body habitus change targeting weight, body mass index,

body fat specially trunk and limb fat, and lipid parameters need to be addressed carefully for individual ART or ART alone and different combinations of ART or HAART. Abnormal fat deposition is not associated with effect of ART alone but examiners also established the relation of trunk fat accumulation with the use of some PIs and limb fat loss with the use of NRTI (21-24). However, combination form of HIV medicines or HAART has shown dramatic immunological cell improvement than ART alone in HIV patients which also leading to abnormal body fat changes along with metabolic abnormalities in parallel way. Previous published direct and indirect meta-analysis explained the effects of HIV-medicines comparing NNRTI based HAART versus PI based HAART considering viral suppression, death or disease progression and withdrawals as outcomes to measure difference before and after treatment intervention in HIV-patients. Direct data analysis suggested that NNRTI based HAART is more effective than PI based HAART for viral suppression with no difference in disease progression for both treatment groups (25). Besides, a systematic review investigated the role of efavirenz (subclass of NNRTI) plus NRTI and efavirenz plus PI on body habitus abnormalities to measure body fats (limb-fat, trunk-fat, visceral, sub-cutaneous and total body fat) along with BMI and weight, where they included nine potential studies (26). In five non-comparative clinical trials, body fat alteration was very low while weight gain was significantly high when patients treated with efavirenz composed of non-thymidine analogues following 144 weeks of treatment. In addition, limb fat gain was higher in non-thymidine analogue than thymidine analogue treated patients. In four comparative trials, limb fat increased in efavirenz treated group along with trunk fat increase in both efavirenz and PI treated groups.

No proven HIV medicines used by the health care providers those could reduce the chance of body habitus abnormalities. The prevalence of excess trunk fat accumulation and loss of limb fat have shown to be significantly associated with disproportionate body fat relation in HIV patients after antiviral treatment. Evidence based research on abnormal fat deposition with weight gain along with obesity prevalence in HIV patients directed us to further investigate on weight, body mass index, body fat constituents and lipid profiles, considering all as an interlinked condition targeting HIV patients receiving antiviral medications. No previous meta-analysis has conducted considering body fat change or, body habitus change. With the urge to intervene more on impacts of HIV medicines on body habitus change this meta-analytic research explored degrees of body habitus changes targeting NRTIs, NNRTIs, PIs and combined forms of HAART as different treatment intervention options in HIV-infected patients and how those effects could vary depending on context and sample characteristics. We will answer what works best, for who and under what circumstances. In addition, this research will direct health care providers to select appropriate HIV medicine for patients maintaining body balance along with minimizing chances of cardiovascular risks.

Research Purpose

The purpose of this study was to evaluate the effects of different ART treatments on body habitus/ body composition among HIV positive patients-meta analyzing the scientific evidence.

Research Objectives/Aims

1. To obtain overall effect sizes of different ART treatments on-
    - Weight, body mass index, trunk fat and limb fat as primary outcome variables.

- Lipid parameters such as LDL, HDL, Total cholesterol and Triglyceride as secondary outcome variables.

2. To explore variability among different ART treatments/interventions considering all treatments clustered within the studies using multilevel approach for meta-analysis.
3. To explain variability and heterogeneity of different ART treatments in all outcome variables along with moderator analysis using study, treatment, and sample characteristics.

We hypothesized that, first, different ART treatment interventions will have impacts/effects, (considering Becker's d equation to calculate effect sizes considering post treatment mean value minus pre-treatment mean value divided by standard deviation of the pre-estimated value for specific outcome) on each outcome variable favoring ART medicines as research hypothesis ($d \neq 0$) and ART medications on body habitus change has no effects as null hypothesis ($d=0$). Second, the studies will illustrate significant variability based on the Q statistics (Q is calculated as the weighted sum of the squared differences between individual study effects and a pooled effect across studies) and the I2 index (I2 statistics describe the percentage of variation across studies due to variability). Third, for multilevel approach, our research hypothesis is that, different ART treatments will be statistically significantly different (χ^2 statistics, Q) from each other indicating $p < 0.05$ for individual outcome. Fourth, multilevel model will explain the amount of significant heterogeneity by treatment and will explain the degree of variability (using Q as unexplained residual variance and I2 as index of unexplained variance) of different effect sizes by treatment irrespectively when we include different moderators into our model.

METHODOLOGY

Systematic Search Procedure

We searched five electronic databases (PubMed, Scopus, CINAHL, PYCHINFO and Cochrane Controlled Trials register) from July 6 to September 8, 2015. With the assistance of an expert librarian in a Public University library, we used specific key words such as “Clinical trial”, “HIV”, “Anti-Retroviral Agents", “Body Mass Index”, “Body fat” with medical subject headings. Detail information regarding “Boolean Search Terms” provided in *appendix-1*. A hand search of references from included studies was conducted to identify any missing study along with the citations published on Journals of AIDS, Current HIV Research.

Identification Criteria

To identify unique studies eligible for our study, we selected papers based on their abstract and full-text if available. Studies were included based on the pre-defined criteria:

- ***Population of interest:*** HIV-infected patients 16 years or older with no previous history of anti-retroviral exposure.
- ***Interventions:*** Studies those had pre-post intervention measurements. Stated following treatments as interventions- Nucleoside Reverse Transcriptase Inhibitor (NRTIs) or, Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs) or, Protease Inhibitor (PIs) or, Combination of Antiretroviral Therapy (HAART) following FDA-Approved HIV-medicines (two NRTIs, three NRTIs, two NRTIs plus one NNRTI (Atripla), two NNRTIs plus one PI, NRTI plus NNRTI, NNRTI plus PI and Ritonavir boosted Lopinavir (LPV/r) or, Kaletra).

- ***Comparisons:*** Compared combined ART such as LPV/r plus NRTI vs NNRTI plus LPV/r or, LPV/r plus other combined ART vs LPV/r alone or, comparisons between PI plus NRTI vs PI plus NNRTI vs NRTI plus NNRTI or, NRTI vs NNRTI vs PI or, comparisons in between subclasses of NRTI, NNNRTI or PI.
- ***Outcomes:*** Body habitus change considering weight, body mass index, trunk fat and limb fat as primary outcomes considering DEXA technique as benchmark to measure trunk and limb fat; and lipid parameters such as LDL, HDL, Cholesterol and Triglyceride as secondary outcomes.

This research excluded studies if assessed on HIV-negative individuals, children, adolescent population and pregnant women. Studies were excluded those stated on patients taking medication for hypertension and diabetes mellitus, those could act as potential confounding variables.

Quality Assessment

Two independent researchers (NH and YC) provided decisions with appropriate justifications for final study selection process based on the selection criteria and based on the screening process of title, abstract and full manuscript. Total twenty unique trials were included for this meta-analysis Figure-1, representing the PRISMA flow diagram of the final study selection process. A comprehensive coding form and manual was created by research team consist of HIV researcher, biostatistician and a physician. The coding form includes approximately 200 variables for each study. Structured coding form was pilot tested by (NH and MC) and was reviewed by third expert (TBHM). Content coding form (*provided in appendix 2*) included information based on study information;

demographic characteristics; ethnicity; anthropometrics such as height, weight, waist circumference, waist-hip ratio, total body fat %, trunk fat, limb fat; metabolic parameters; lipid parameters such as LDL, HDL, cholesterol, triglyceride; route of HIV transmission: homosexual, heterosexual, blood contamination; stages of HIV infection following CDC stages; number of patients at the beginning and end of trial along with specific criteria for lost follow up; intervention characteristics; methodological quality; type of HIV-medicines used as treatment interventions and risk of bias Table-1 explained information on study characteristics, number of patients, duration, demographics and type of ART used as ART treatments along with comparison groups of twenty included literatures. Two independent researchers (NH and YC) collected data separately. After data collection inconsistencies were resolved by an expert professional (TBHM)

DATASET PREPERATION

Included studies showed multiple treatment comparisons and comparisons varied from one study to another. We dummy coded and created sub category of HIV medicines for appropriate analysis purposes those attached in Appendix-3. We created sub classes for combination ART regimens. NRTI which compared alone with other ART was categorized as category 1. NNRTI alone, that compared with other ART considered as category 2. PI alone compared with other drugs considered as category 3. We found that, five studies considered and compared ritonavir boosted Lopinavir (LPV/r which is FDA approved HIV medicines under combination category) with other types of ART and we coded them as LPV/r containing combination category 4. PI medicines used in combination with ART and compared with combination ART drugs as PI containing combination ART category 5. NNRTI used along with combination ART and compared with different ART drugs as NNRTI containing combination ART category 6.

STATISTICAL ANALYSIS

Inter rater reliability (IRR) was calculated for all continuous and categorical variables using IBM SPSS Statistical Version 22 (28). The kappa (κ) coefficient was 0.94, resembling 94% agreement for categorical variables and agreement for Pearson's correlation coefficient r =0.98 for numerical variables (29-30). For publication bias, we assessed asymmetries by using Begg, Egger, trim and fill statistical tests along with funnel plots. Publication bias was calculated and graphical statistics were plotted using R version 3.2.2 "metafor" package.

Using effect size calculator created by Huedo-Medina, effects for targeted outcomes were calculated (31). Standardized mean change following Becker's d equation shown below, was used to calculate the effect sizes as all outcome variables were continuous where standardized mean changes were the difference between the post-test and pre-test means for one sample, divided by the pre-test or post-test standard deviation. Standardized mean change was considered as effect size index that follows a normal distribution with a range from negative infinity to positive infinity which allows results from several designs to be compared and combined directly (32).

Becker's d equation: $d = \frac{M_{post} - M_{pre}}{SD_{pre}}$

To interpret effects on targeted outcomes, standardized d value can be classified as 0.25, 0.5 and 0.8 representing small, medium and large effects following Cohen's classification. (Citation) Weighted mean effect size was calculated which weighted by the inverse of the variance of each study. As all included studies were not identical in their methods, we calculated random effects using random effects model assuming if, data is coming from different populations which controls for different samples and accounts for within and between study variances (33). To test heterogeneity, Q statistics and I2 index were calculated where Q represents significance of heterogeneity and I2 calculates the magnitude of heterogeneity for each treatment. (Ref)

As this meta-analysis included 20 randomized trials with varying type of ART regimens, we assumed that all different ART treatment options are nested within studies and considered multilevel modeling approach. Statisticians described that for multiple-treatment study, two or, more treatment groups could be compared with one single group considering as control (38). For multilevel modeling, we created subsample from the

original dataset for studies those reported same outcome of interest. As multilevel modeling is designed to analyze variables from different levels, using statistical model that properly includes the various dependency issues (39), the purpose of conducting this multilevel meta-analysis was to observe within and between variations in both study levels and treatment levels for each outcome variable. For analysis, we used "metafor" package in R software (40). We used mixed effects models for the multilevel meta-analysis that controls for multiple comparisons using maximum likelihood (ML) method. To estimate degree of overall effect size change by each treatment, we consider *B*-coefficient which indicates how much the overall effect size decreased or, increased moving from the reference combination to the target combination. We considered chi-square statistics to measure over all treatment variation when $p<0.05$. Q and its p value infer if the unexplained variance is still significant. We used "mods" command in R software for moderation analysis to assess the relationship between study level covariates and effect sizes. The goal of the analysis was to examine to what extent the moderators included in the model influence the size of the average true effect (34). In addition to testing the impact of covariates for statistical significance, it is important to quantify the magnitude of their relationship with effect size. For this purpose, we used an index based on the percent reduction in true variance, analogous to the R^2 index with primary studies (35). To represent the relationship graphically we also performed plots using the moving constant technique explained by T. B. Huedo-Medina and the research team (36-37). Using restricted maximum likelihood (REML) method we added "Number of weeks" or, intervention period as moderator.

RESULTS

Total participants were 2,592 HIV-infected positive population. Out of 2,592; 62 people lost follow up, 829 withdraw the treatment, 976 discontinued, 135 patients reported toxicity and number of death report was 12. Mean age was 40.99± 3.07 (mean ±SD) years, 80.4 % were male and 19.6% were female. Out of 20, 6 studies reported on ethnicity, among 1010 participants, 35.97 % were black, 64.03 % were non-Hispanic white. Mean CD-4 cell count was 363.57 ± 188.16 with intervention period of 84.4 weeks. No significant asymmetry found for publication bias when begg's and egger's tests were performed to assess both inferential and graphical statistics which is provided in Table (2-6).

Random effects assumptions explained that body composition components weight increased for individual NRTI and PI treatment groups, LPV/r combination therapy but significantly (p= 0.0009) increased in LPV/r combination category [d+ = 0.44, 95% CI (0.18 to 0.71)]. Body mass index increased in HIV patients when they were treated with individual NRTI and all three combination forms of HIV treatments (LPV/r, PI and NNRTI combination HAART) but significantly (p= <0.0001) increased in LPV/r combination therapy category [d+ = 0.94, 95% CI (0.53 to 1.3)] only. Trunk fat increased significantly (p=0.005) in NRTI alone treatment group with mild effect [d+ = 0.27, 95% CI (0.06 to 0.49)] and limb-fat increased in all treatment groups but significantly increased (p= <0.0001) in PI combination therapy with moderate efficacy [d+ = 0.44, 95% CI (0.26 to 0.63)].

For lipid parameters, HDL increased for all treatment groups but significantly increased when patients received all combination ART or, HAART (LPV/r, PI and

NNRTI) with moderate to high efficacy [d+ = 0.75, 95% CI (0.40 to 1.09)], [d+ = 0.42, 95% CI (0.06, 0.78)] and [d+ = 0.85, 95% CI (0.54 to 1.15)] respectively. Level of LDL or, bad cholesterol reduced in NRTI and PI alone treatment groups and PI combination HAART group but did not reduced significantly after interventions. To observe the overall effect sizes either favoring the baseline or, favoring different ART interventions, we used forest plots to draw graphical relations provided in Figure (8- 13).

Our result on multilevel analysis clarifies that estimates for HDL were statistically significantly different in combination ART (LPV/r, PI and NNRTI) with p= <0.0001, p=0.0130, p= <0.0001respectively. For LDL, estimates were significantly different in NNRTI, LPV/r combined ART and NNRTI combined HAART. In addition, multivariate estimates for triglyceride were statistically significantly different for both alone and in combination HAART with p=<0.0001 for NRTI, p=<0.0001 for NNRTI, p=0.0038 for LPV/r combined HAART, p= <0.0001 for PI combined HAART and p=<0.0001 for NNRTI combined HAART, except for PI alone category. For trunk and limb-fat, variations were statistically significantly different in PI group and NNRTI combination HAART group, with corresponding p=<0.0001. Detail information is provided in Table-12.

From the result output, it represents that intervention period or "number of weeks" act as a strong moderator for LDL [(β= -0.0049), 95% CI (-0.0079, -0.0018)] with significance level of p=<0.0001 indicating that if patients receiving treatment for long time LDL is reduced by 0.0049 units. For body fat constituents, our moderator analysis revealed that, level of trunk and limb fat increases [(β= (0.0033), 95% CI (-0.0020, 0.0086)] and [(β= (0.0025), 95% CI (-0.0040, 0.0090)] as length of HIV

medication/number of week increases, but not significantly. Figure (2-7) for meta-regression plots provided moderation pattern with solid dark red regression line and 95% confidence band under mixed-effects assumptions.

To evaluate the progress of research focusing on body habitus change considering limb fat loss/lipoatrophy a big concern due to prolong ART use, we considered "Publication Year" as moderator variable and found that, limb fat increased 0.063 units and we could interpret that, due to the research advancement limb fat increased [(β=0.0639), 95% CI (0.006, 0.12)] with p= <0.0001 when patients received HIV treatment. For lipid parameters, Publication Year has significant moderation effects on HDL, LDL and TG variables [(β =-0.06), 95% CI (-0.01, -0.02)], [(β =-0.005) 95% CI (-0.007, -0.001)] and [(β =-0.069), 95% CI (-0.11, -0.02)] with p=<0.0001, p=0.002 and p<0.0001 respectively. We did not find significant effects on weight and BMI while we use "Publication Year" as moderator into out model.

Female patients act as a strong moderator variable for HDL and LDL. Mixed effects models explained that, level of HDL and LDL decreases [(β=-0.006), 95% CI (-0.01, -0.0015)], [(β=-0.01), 95% CI (-0.019, -0.005)] significantly (p=<0.0001), if the number of female population increases, followed by no significant moderation effects on weight, BMI, trunk fat, limb fat, cholesterol and TG.

Average mean age of HIV patients also acts as a strong moderator variable for cholesterol [(β=-0.17), 95% CI (-0.23, -0.10)] and TG [(β=-0.07) 95% CI (-0.11, -0.04)], pointing that, level of blood cholesterol and TG decreases due to the aging process.

Methodological quality score has significant (p=<0.0001) moderation effect on Limb fat variable only and we can explain that, level of limb fat increases [(β = 0.18),

95% CI (0.005, 0.36)] in the studies those followed appropriate methodology or, maintained research quality. Criteria to assess quality of a study need to be addressed carefully to improve methodological quality score which might act as a strong moderator to impact on other targeted outcome variables. In-detail information is provided in Table-13. List of moderators with no significant results and variables unable to use as moderators due to lack of study reports are also provided in Table (14-15).

DISCUSSION

This meta-analysis of randomized clinical trials was uniquely able to assess changes in weight, body mass index, trunk fat limb fat and lipid parameters considering both individual (NRTI, NNRTI, PI) treatment category and three combination HAART following FDA approved classifications of HIV medicines.

Five studies provided pre-post data on weight. Overall, effect sizes indicated that body weight tends to increase in NRTI alone group, PI and LPV/r combination HAART groups in mild to moderate extents after intervention but did not increased significantly. Out of twenty, six studies quantified body mass index data after ART therapy with no study reports on overweight or, obesity. For waist circumference, seven studies reported baseline information on waist circumference but only three studies reported on post ART intervention data. We could not be capable to get different ART effects on waist circumference and waist-hip ratio due to lack of study reports. Body mass index increased after intervention in NRTI alone group, LPV/r combination, PI combination and NNRTI combination HAART categories but did not increased significantly. We, therefore, can state that decent increase of weight and BMI is beneficial for HIV infected

patients as wasting is a huge concern in HIV patients. It could have been alarming if we get significant increase on weight and BMI, which could be indicative and supportive of the prevalence of overweight and obesity in HIV- patients.

For trunk-fat, eleven studies reported on pre-post assessments. Trunk fat did not increase significantly after intervention for all ART regimens except for individual NRTI. Total ten studies reported on limb-fat. Our study results showed significant increase on limb-fat when patients were NRTI alone and PI combination HAART category. For total body fat measure, eight studies provided post data and we found that, total body fat increased significantly in NRTI and LPV/r combination HAART categories.

For lipid parameters, HDL which is considered 'good cholesterol' increased in all ART regimens, but significantly increased in NNRTI combination ART with high efficacy. LDL decreased after intervention in NRTI and PI alone treatment categories. Triglyceride levels decreased significantly after intervention those received PI alone group. In the moderator analysis, we found that the number of weeks has negative effect on LDL, indicating that, as number of weeks increased, the level of LDL decreased significantly in NRTI and PI alone groups. We can stablish our first and second hypothesis that, all treatment groups have impacts on weight, BMI, trunk fat, limb fat, lipids as part of body habitus and able to explain the variability.

For the multilevel meta-analysis, impacts of NRTI alone, PI alone and LPV/r combination HAART categories differ significantly for weight and three combination groups differ significantly for body mass index (BMI). Effect size for HDL was statistically significantly different while patients were receiving LPV/r, PI and NNRTI combination HIV medications. For LDL, effect size was significantly different between

LPV/r and NNRTI combination therapy categories and NNRTI alone category. In addition, effect size was significantly different in LPV/r combination and NNRTI combination HAART categories for cholesterol. For triglyceride, impacts of all ART groups were significantly different except PI alone group. LPV/r and NNRTI combination form of antiviral medications were statistically significantly different from each other for trunk and limb fat. Thus, we can comply our third hypothesis that, formed ART treatments groups were statistically significantly different from each other considering all outcome variables.

We included treatment period or, length of intervention as weeks, publication year, mean age, female gender, proportion of white population, methodological quality as potential moderators to perceive how much they modify the result when included into our multilevel moderation model. From results, we can infer that intervention period has a significant moderation effect on LDL only. Publication year displayed significant moderation effect on limb fat, HDL, and triglyceride. In addition, female gender modified HDL and LDL significantly, mean age of HIV patients has significant moderation effects on cholesterol and triglyceride, proportion of white population has significant moderation effect on trunk fat, limb fat, cholesterol and methodological quality modified only limb fat. From our study, we were not able to clarify moderation effects on weight, BMI, considering variables as potential moderators and unable to stablish our fourth research hypothesis.

We collected information if studies conveyed information on mode of HIV infection. Total seven studies reported on route of HIV transmission. As different mode of HIV spread, six studies reported on homosexual character/patients having sex with

same gender, five studies reported on heterosexuality, three studies reported proportion of population used drugs. As risk characteristics/comorbid health status, we considered high blood pressure as one of major cardiovascular disease condition, diabetes and smoking habits. Three studies reported on diabetes, one study reported on smoking and no studies reported on blood pressure measures. It could have been interesting to perceive the moderation effects of specific moderators on weight, BMI, body fats and lipid parameters to help reduce the chances of chronic associated health fatalities in HIV patients as HIV itself leads to life threatening conditions in the long run if not treated properly.

Risk of Bias

Out of twenty included studies, nine reported on random sequence generation and allocation concealment. For blinding of participants, 10 studies reported on open label resembling of "high risk of bias"; three studies reported on single blinding; two studies reported on double blinding; 4 studies did not report on blinding of participants and reported as "unclear". One study was blinded at the beginning but un-blinding done by data safety and monitoring board. Two studies reported on blinding of outcomes, two studies reported on incomplete outcome data, one study on selective reporting and no studies reported on other bias category considering Cochrane criteria for judging Risk of Bias (24). Cochrane risk of bias is provided in Figure-14. Study design and protocol can be improved and addressed properly as randomization, allocation, blinding are important constructs in investigating the effects of methodological quality.

Strengths and Limitations

This is the first meta-analysis that considered body habitus change targeting weight, body mass index, trunk fat and limb fat along with lipid parameter change after antiviral

treatment considering randomized clinical trials. We consider randomized controlled trials (RCTs) the best experimental design with less vulnerability to bias. This is an extension of classical meta-analysis that considered multilevel approach, which explains variability within and between studies in addition to help distinguishing differences in treatment levels considering different moderators for individual outcome variable. Moreover, this study considered FDA approved drug classifications which were last updated in 2015 and this helped our research team to create a sub class for combination forms of antiviral medicines or, HAART.

One possible limitation is due to time constraints, we were not able to collect raw data, as this would require too much time to contact study authors and few studies reported median value but not the mean value and we calculated the mean which might not be reliable to some extent. Secondly, three studies reported switching ART due to drug dose adverse effects during the intervention period and we could not be able to control that while analyzing data. Thirdly, we could not include five potential studies due to lack of appropriate data representations, as we did not hear back from authors requesting to get information of our variables of interest. It could have different impact on our result output along with the increase quantity of total sample size. In addition, due to lack of proper drug dose information, we could not include and compare ART regimens across specific dosages. This study might have been more informative if we could include different ART regimens along with dose information to observe specific drug dose effects on different outcomes before and after intervention.

CONCLUSIONS

Our research team tried to explain degree of body habitus change by providing the extent of efficacy of each ART on weight, body mass index, limb fat, trunk fat and lipid parameters. Per our results, we can conclude that, different ART treatment interventions had different impacts on each outcome variable. LPV/r containing combination therapy is more beneficial for weight and BMI improvement. HIV patients those received combination ART along with protease inhibitors (PIs) had moderate beneficial effect on limb fat improvement than those were in other ART medications. For HDL, all three combination forms of ART are efficacious, but combination form of HIV medicines along with NNRTI exhibited high efficacy for HDL. For multilevel approach, each outcome variable was statistically significantly dissimilar from different treatment groups along with the significant heterogeneity by treatments. We also explained the degree of variability including publication year, number of weeks, number of female, methodological quality and average mean age as moderators and identified the statistic of residual variance and degree of residual variance those are still unexplained.

In future direction, this study aims to conduct a network meta-analysis considering multiple ART regimens for comparing both direct comparisons of interventions with randomized trials and indirect comparisons across trials based on a common comparator.

RESEARCH CONTRIBUTIONS

This study provided evidence to the HIV care providers addressing impacts of different antiretroviral medications in HIV patients emphasizing body habitus change as a sophisticated issue. Careful ART treatment is needed by establishing specific treatment protocol depending on severity of HIV infection while conducting ART interventions to minimize ART related fatal conditions and maintain body balance in HIV patients.

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FIGURES

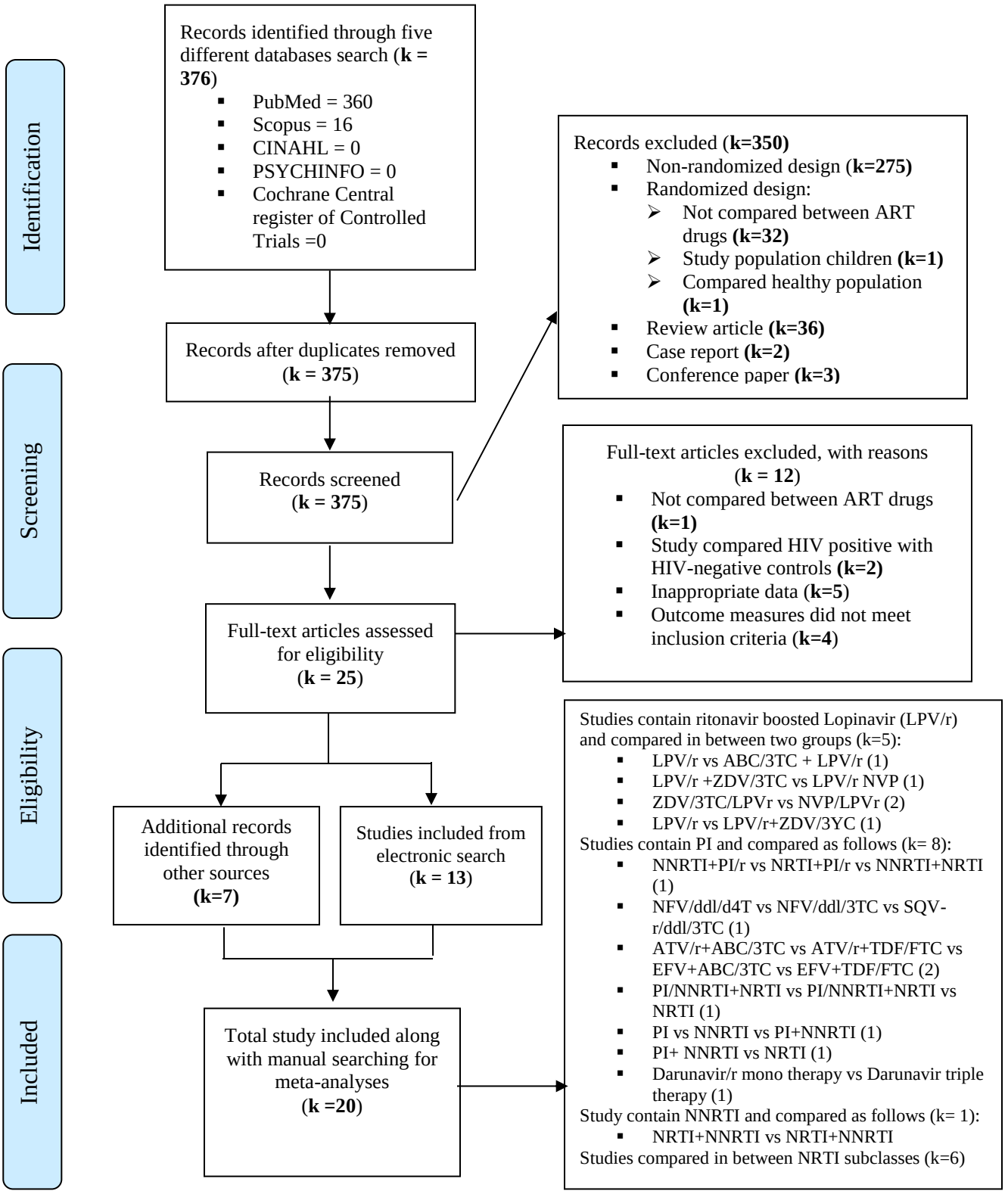

Figure 1: Study identification and selection process using PRISMA diagram

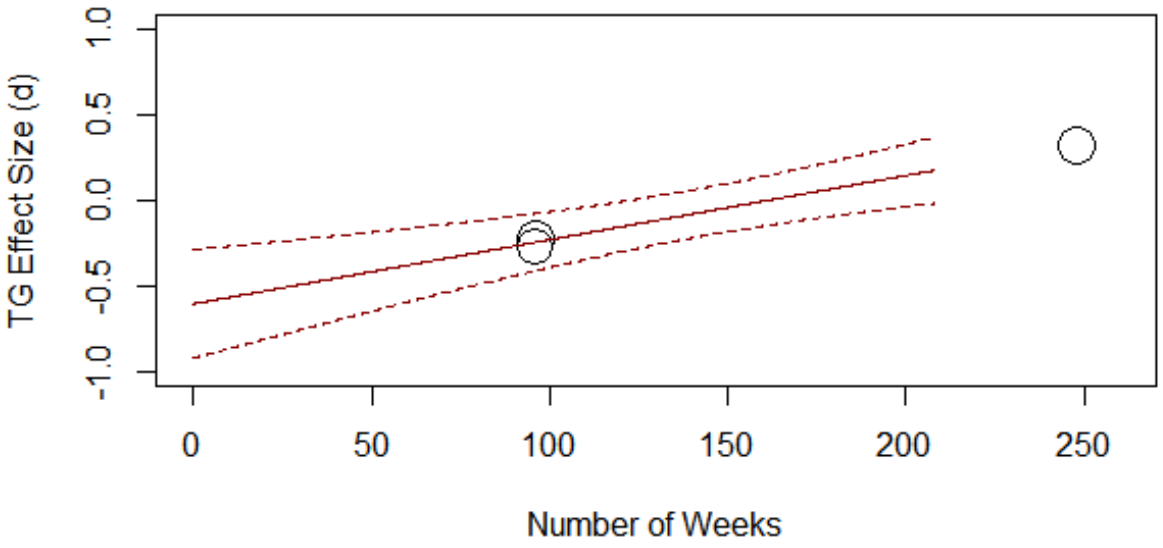

Figure 2: Meta Regression plot for TG in PI regimen.

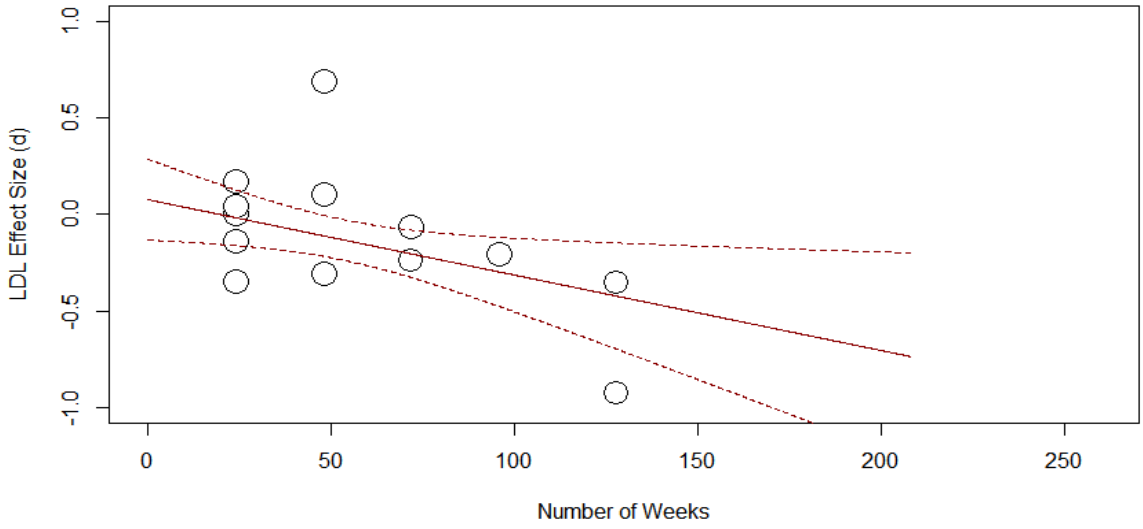

Figure 3: Meta Regression plot for LDL in NRTI regimen.

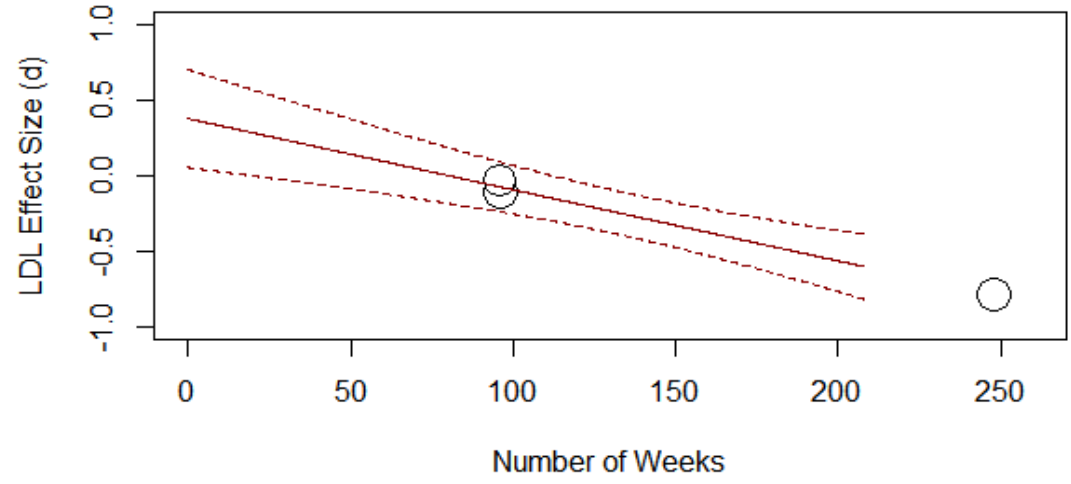

Figure 4: Meta Regression plot for LDL in PI regimen.

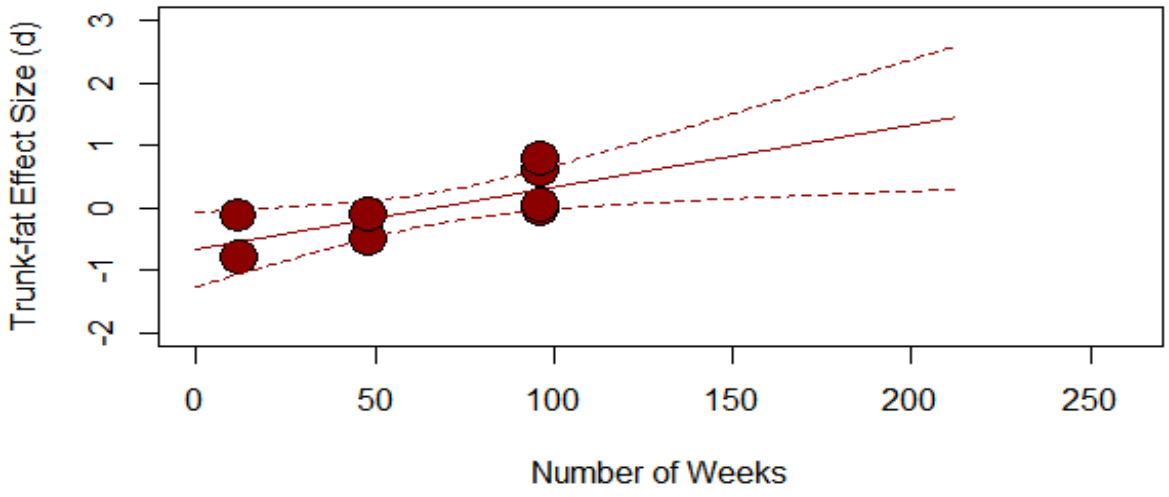

Figure 5: Meta regression plot for Limb fat in LPV/r combination category 1.

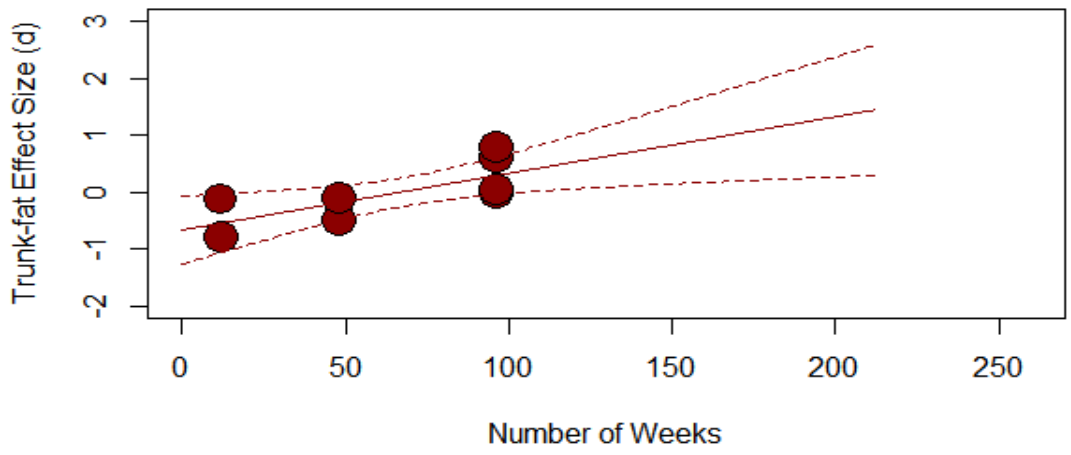

Figure 6: Meta Regression plot for Trunk-fat in LPV/r combination HAART category 1.

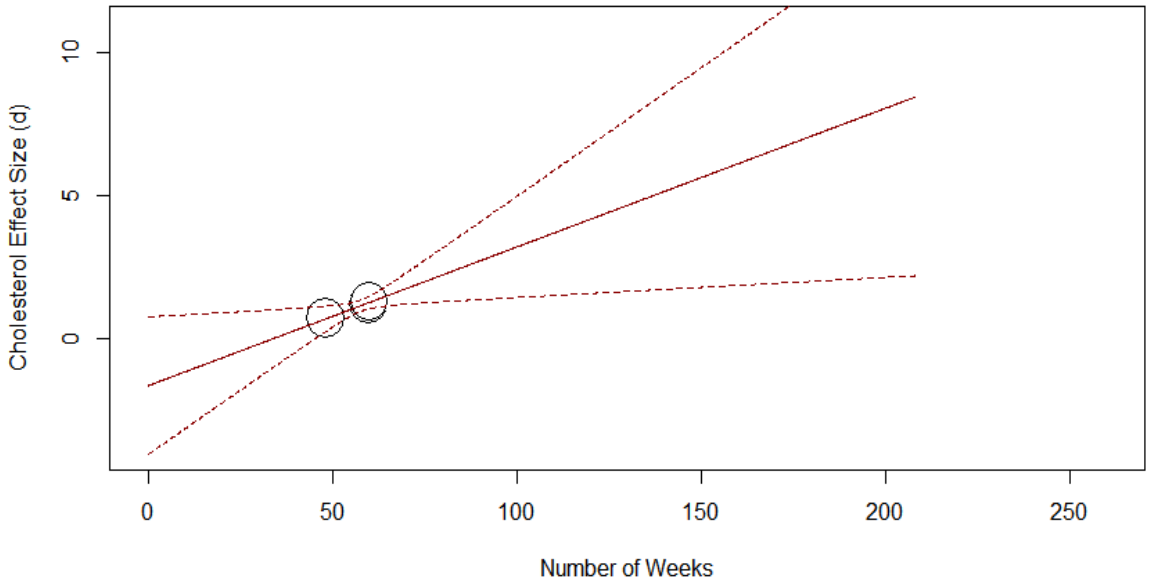

Figure 7: Meta regression plot for Cholesterol in NNRTI combination HAART category 3.

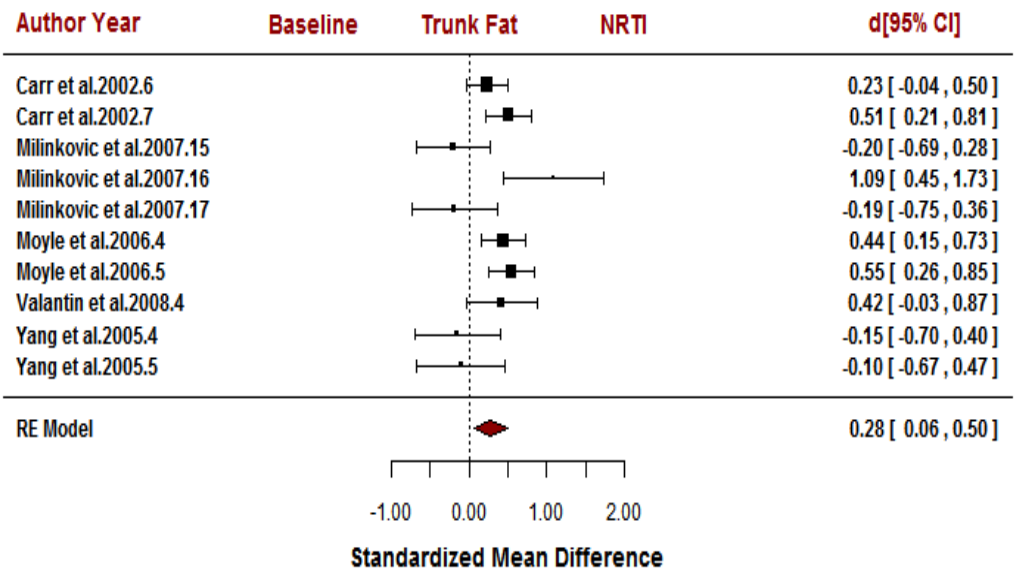

Figure 8: Forest plot for Trunk Fat favors NRTI regimen

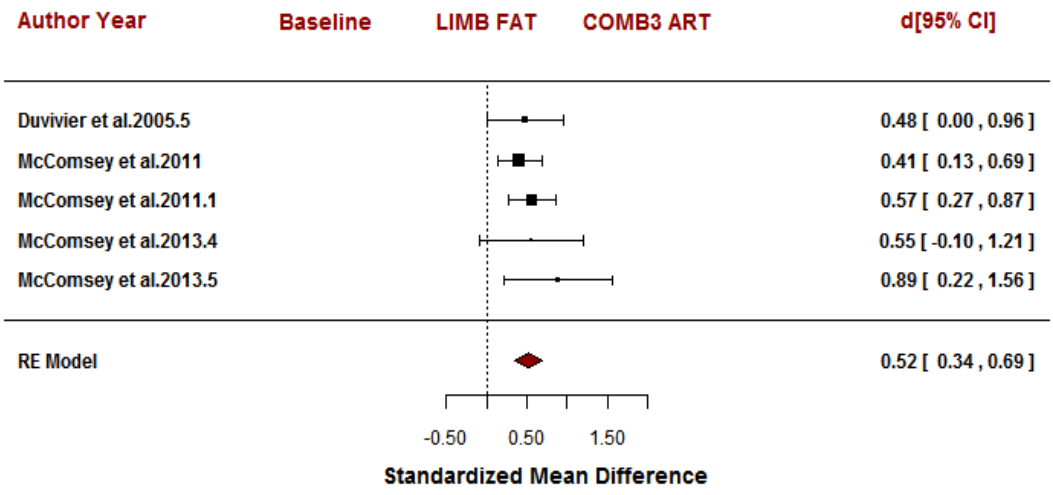

Figure 9: Forest plot for Limb Fat Favors NNRTI Combination HAART category 3.

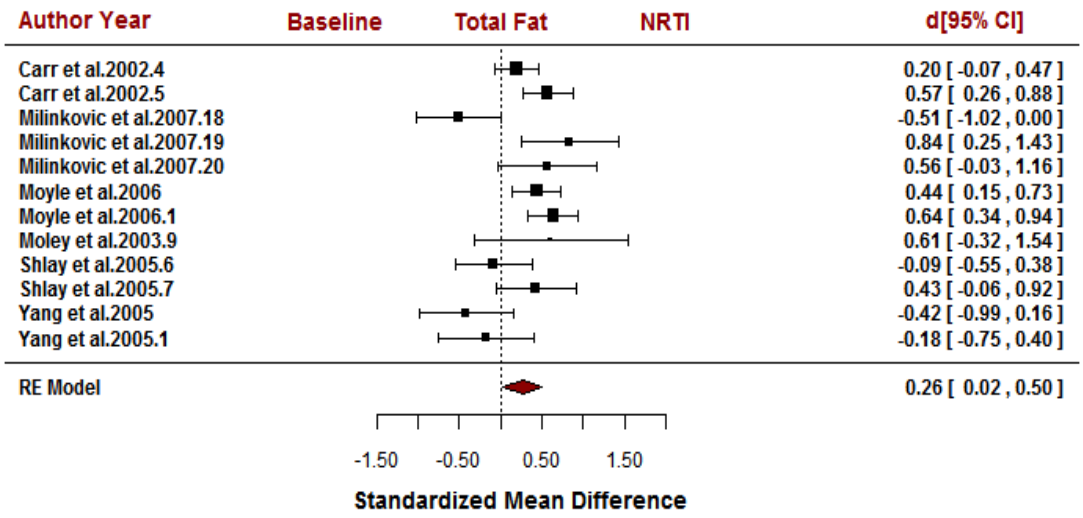

Figure 10: Forest plot for Total body fat favors NRTI

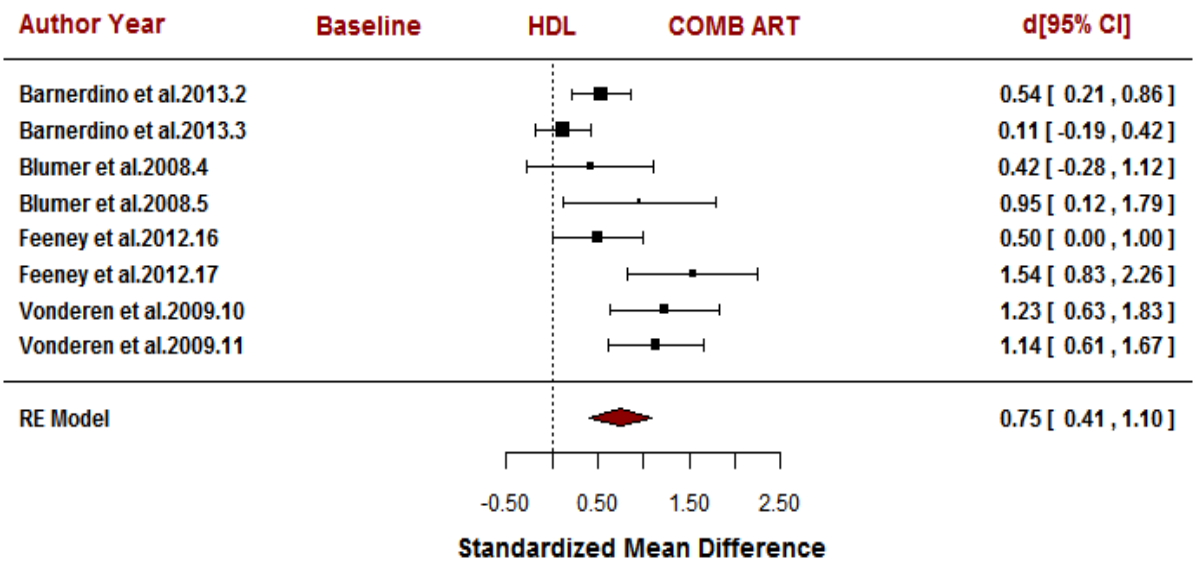

Figure 11: Forest plot for HDL favors LPV/r Combination HAART category 1

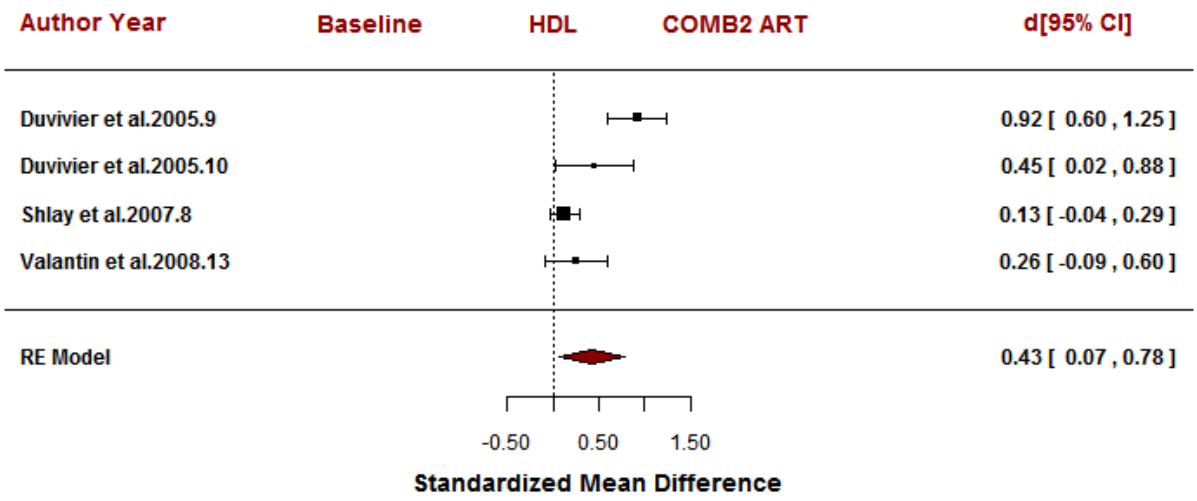

Figure 12: Forest plot for HDL favors PI Combination HAART category 2

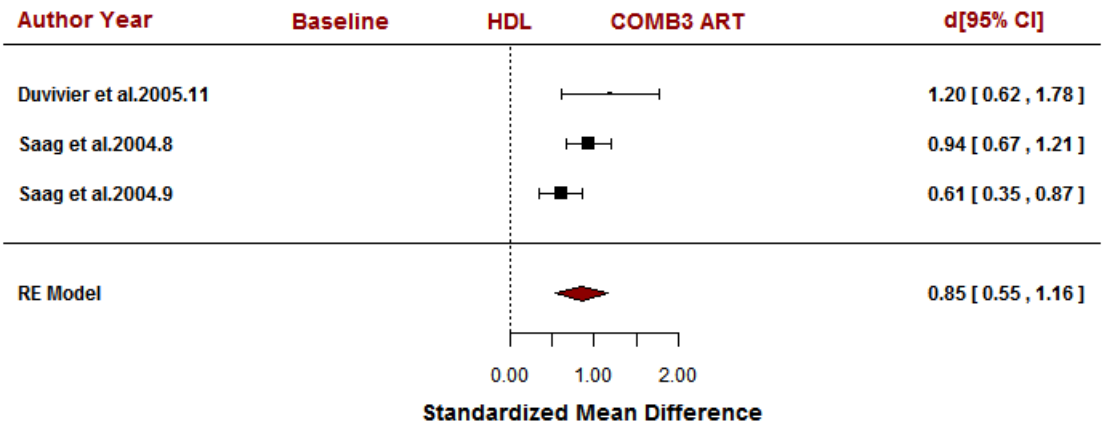

Figure 13: Forest plot for HDL favors NNRTI Combination ART category 3

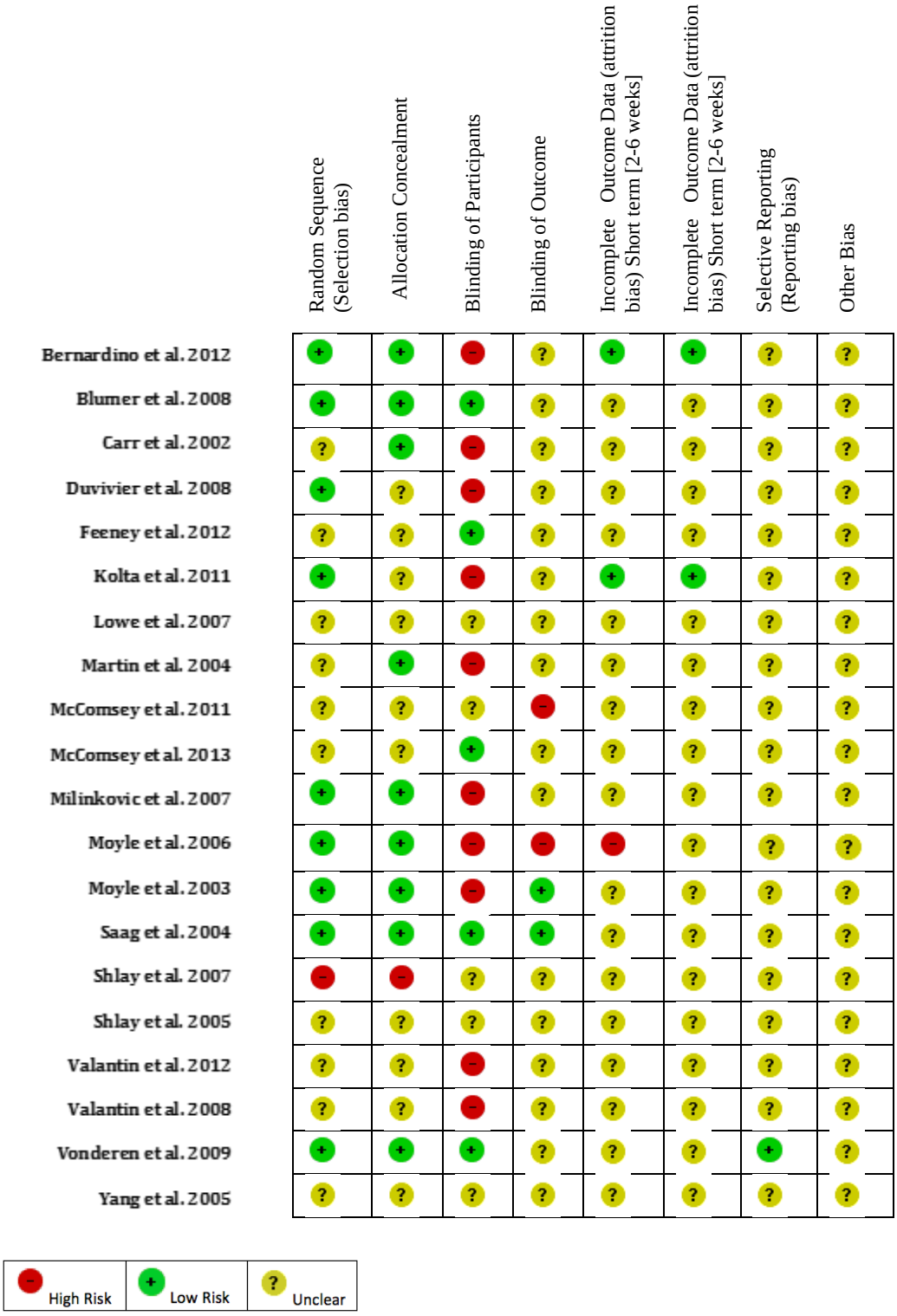

Figure 14: Cochrane Risk of Bias Table

TABLES

Table 1: Summary of Included Literatures

Author, year of publication	Study duration	Number of patients assessed	Demographics	Number of intervention groups along with treatment type
Bernardino et al. 2012	96 weeks	88	Median age: 44.8 years Male: 59 (67%); Female: 29 (33%) Ethnicity: Not reported CD4 cell count: 697 median Toxicity reported: 13	A. LPV/r monotherapy B. ABC/3TC + LPV/r triple therapy Total two groups
Blumer et al. 2008	12 weeks	20	Median age: 42 years Male: 20 (100%) Ethnicity: Not reported CD4 cell count: 200 median Toxicity reported: 2	A. LPV/r + ZDV/3TC B. LPV/r + NVP Total two groups
Carr et al. 2002	24 weeks	111	Median age: 43.5 Male: 105 (94.59%); Female: 6(0.05%) Ethnicity: Not reported CD4 cell count: 578.5 Toxicity reported: 4	A. Stavudine/Zidovudine B. AbacavirA Total two groups.
Duvivier et al. 2008	48 weeks	117	Median age: 37.3 years Male: 87(74%); Female: 30(26%) Black: 42% CD4 cell count: 207 median CDC stage not reported	A. NRTI containing regimen: PI/r plus two NRTI Or, NNRTI plus two NRTIs B. NRTI-sparing regimen: NNRTI plus boosted PI/r. Total three groups.
Feeney et al. 2012	144 weeks	48	Median age: 59.5 years Male: 48(100%) White race: 81% CD4 cell count: 212.5 median CDC stage reported Toxicity reported: 10	A: NRTI containing regimen ZDV/3TC with LPV/r B: NRTI-sparing regimen NVP with LPV/r. Total two groups.

Kolta et al. 2011	48 weeks	136 DEXA data contain subsample of 63 patients	Mean age: 36 years Male: 89(65.44%); Female: 47(34.56%) Ethnicity: Not reported CD4 cell count: 238.5 mean	A. LPV/r Monotherapy B. LPV/r+ZDV/3TC Total two groups
Lowe et al. 2007	96 weeks	19	Median age: 43.73 years Male: 16 (84.21%); Female: 3(15.79%) Ethnicity: Not reported CD4 cell count: 173.33 median	A. NFV/ddl B. NVP/ddl/3TC C. SQV-r/ddl/3TC Total three groups
Martin et al. 2004	72 weeks	111	Median age: 43.5 Male: 105 (94.59%); Female: 6(5.41%) Ethnicity: Not reported CD4 cell count: 578.5 Toxicity reported: 4	A. ZDV/d4T B. Abacavir Total two groups
McComsey et al. 2011	96 weeks	269	Median age: 38 years Male: 229(85%); Female: 40(15%) White (Non-Hispanics): 47% CD4 cell count: 233 median Toxicity reported: 44	A. EFV+TDF-FTC B. EFV+ABC-3TC C. ATV-rtv + TDF-FTC D. ATV-rtv + ABC-3TC Total four groups
McComsey et al. 2013	96 weeks	56	Median age: 39 years Male: 49(87%); Female: 7(13%) White (Non-Hispanics): 39% CD4 cell count: 227 median	A. ABC/3TC B. TDF/FTC C. EFV D. ATV/r Total four groups
Milinkovic et al. 2007	24 weeks	58	Median age: 43 years Male: 54 (93.10%); Female: 4(6.90%) Ethnicity: Not reported CD4 cell count: 587 median Toxicity reported: 1	A. d4T40 B. d4T30 C. TDF Total three groups
Moyle et al. 2006	48 weeks	105	Mean age: 42.5 years Male: 95 (90.47%); Female: 10(9.53%) Ethnicity: not reported CD4 cell count: 503.5 Toxicity reported: 4	A. Tenofovir DF B. Abacavir Total Two groups
Moyle et al. 2003	48 weeks	30	Mean age: 42 years Male: not reported White:	A. d4T with ABC B. PI or NRTI with ABC

			CD4 cell count: 540.5 Toxicity reported: 1	C. d4T and PI or NNRTI with ABC+AZT Total three groups
Saag et al. 2004	60 weeks	571	Mean age: 36.15 years Male: 485 (84.93%) Female: 86 (15.07%) Ethnicity: Toxicity reported: 56	A. ZDV/d4T B. Abacavir Total two groups
Shlay et al. 2007	248 weeks	422	Mean age: 38 years Male: 333 (79%) Female: 89(21%) Black: 60% CD4 cell count not reported	A. PI B. NNRTI C. PI+NNRTI Total three groups
Shlay et al. 2005	128 weeks	96	Mean age: 36.5 years Male: 69(71.9%) Female: 27(28.1%) Black: 63.5% CD4 cell count: 237 median	A. ddI+d4T B. ABC+3TC Total two groups.
Valantin et al. 2012	96 weeks	156	Median age: 45 years Male: 121 (77.6%); Female: 35(22.4%) Race: Not reported Baseline CD4 cell counts: Not reported	A. Darunavir/r monotherapy B. Darunavir/r triple therapy Total two groups.
Valantin et al. 2008	96 weeks	100	Median age: 44.5 years Male: 79(79%); Female: 21 (21%) Homosexuals: 51% CD4 cell count: 610 median CDC stage reported Toxicity reported: 18	A. NRTI maintaining group B. NRTI sparing regimen NNRTI and PI Total two groups.
Vonderen et al. 2009	96 weeks	50	Median age: 40.5 years Male: 50(100%) White: 81% CD4 cell count: 212.5 median Toxicity reported: 7	A. ZDV/3TC/LPV/r B. NVP/LPV/r Total two groups
Yang et al. 2005	72 weeks	29	Mean age: 42.45 years Male: 21 (72.41%); Female: 8 (27.59%) Ethnicity: Not reported CD4 cell count: 552.5 mean	A. ER B. IR Total two groups

Table 2: Publication Bias for NRTI

Outcome	S	Begg's	Egger's
Weight	3	1	0.5259
BMI	3	0.3333	0.1745
Trunk-fat	10	0.7275	0.2908
Limb-fat	8	0.7195	0.3846
Total Body fat	12	0.7373	0.3638
Cholesterol	11	1	0.9925
HDL	12	0.6384	0.3821
LDL	13	0.5900	0.7326
TG	13	0.9524	0.0956

Table 3: Publication Bias PI

Outcome	S	Begg's	Egger's
Weight	Won't run		
BMI	No data		
Trunkfat	Won't run		
Limbfat	Won't run		
Total Body fat	Won't run		
Cholesterol			
HDL	3	1	0.4416
LDL	3	1	0.2044
TG	3	1	0.4297

Table 4: Publication Bias Combined Drug Category 1

Outcome	S	Begg's	Egger's
Weight	4	0.75	0.7444
BMI	2	1	N/A
Trunkfat	8	0.9049	0.9076
Limbfat	4	1	0.3024
Total Body fat	6	0.0167	0.0386
Cholesterol	8	0.1789	0.008
HDL	8	0.1789	0.0452
LDL	8	0.0610	0.012
TG	8	0.0610	0.0021

Table 5: Publication Bias Combined Drug Category 2

Outcome	S	Begg's	Egger's
Weight	WON'T RUN		
BMI	5	0.0833	0.0473
Trunkfat	6	0.4694	0.0290
Limbfat	10	0.2912	0.3144
Total Body fat	2	1	N/A
Cholesterol	5	0.2333	0.2940
HDL	4	0.7500	0.3432
LDL	6	0.2722	0.5953
TG	6	0.4694	0.2602

Table 6: Publication Bias for ART Combined Drug Category 3

Outcome	S	Begg's	Egger's
Weight	2	1	N/A
BMI	5	0.8167	0.4433
Trunkfat	2	1	N/A
Limbfat	2	0.2333	0.2625
Total Body fat	3		
Cholesterol	3	1	0.2712
HDL	3	0.3333	0.5442
LDL	3	0.3333	0.0548
TG	3	1	0.6178

Table 7: Overall Effect Sizes (RE) and Homogeneity assumptions for NRTI alone

Outcome	*k*	d (95% CI)	Homogeneity of effect sizes		I^2 (95% CI)
		Random-Effects	*Q*	*P-value*	
Weight	3	0.20 (0.03, 0.37)	0.23	0.88	0
BMI	3	0.20 (0.03, 0.37)	0.07	0.96	0
Trunk fat[a]	10	0.27 (0.06, 0.49)	23.39	0.005	65.74
Limb-fat	8	0.18(-0.27, 0.65)	40.21	<0.0001	87.60
Total Body Fat[a]	12	0.26 (0.02, 0.50)	34.69	0.0003	72.71
Cholesterol	11	-0.04 (-18, 0.09)	17.26	0.06	39.34
HDL	12	0.002 (-0.11, 0.12)	15.29	0.16	25.00
LDL	13	-0.13(-0.24, 0.02)	17.50	0.13	14.35
TG	13	-0.02 (-0.12, 0.07)	0.002	0.002	0.02

[a] Significant Outcomes

Table 8: Overall Effect Sizes (RE) and Homogeneity assumptions for PI alone

Outcome	*k*	d (95% CI)	Homogeneity of effect sizes		I^2 (95% CI)
		Random-Effects	*Q*	*P-value*	
Weight[a]	2	0.32 (-0.08, 0.72)	5.99	0.01	83.32
BMI	No data				
Trunk fat	2	0.46 (0.29, 0.63)	0.49	0.48	0
Limbfat	2	0.27 (0.11, 0.43)	0.24	0.61	0
Total Body Fat	No data				
Cholesterol	2	0.06 (-0.10, 0.22)	0.18	0.67	0
HDL	3	0.05 (-0.13, 0.24)	3.89	0.14	48.75
LDL[a]	3	-0.30 (-0.76, 0.15)	18.13	0.0001	90.30
TG[a]	3	-0.05 (-0.42, 0.31)	13.42	0.0012	85.71

[a] Significant Outcomes

Table 9: Overall effect sizes (RE) and homogeneity assumptions for LPV/r combination category

Outcome	*k*	d (95% CI)	Homogeneity of effect sizes		I^2 (95% CI)
		Random-Effects	*Q*	*P-value*	
Weight[a]	4	0.44 (0.18, 0.71)	3.34	0.0009	14.49
BMI[a]	2	0.94 (0.53, 1.34)	0.01	<.0001	0.00
Trunk-fat	8	0.01 (-0.31, 0.34)	29.34	0.91	79.16
Limb-fat	4	0.10 (-0.31, 0.52)	15.24	0.61	82.68
Total Body Fat[a]	6	0.39 (0.12, 0.65)	12.76	0.003	61.97
Cholesterol[a]	8	0.64 (0.21, 1.07)	42.30	0.003	82.34
HDL[a]	8	0.75 (0.40, 1.09)	25.78	<.0001	72.63
LDL[a]	8	0.69 (0.20, 1.18)	45.93	0.005	86.78
TG[a]	8	0.56 (0.14, 0.98)	38.61	0.008	82.20

[a] Significant Outcomes

Table 10: Overall effect sizes (RE) and homogeneity assumptions for PI combination category

Outcome	*k*	d (95% CI)	Homogeneity of effect sizes		I^2 (95% CI)
		Random-Effects	*Q*	*P-value*	
Weight	1	(FE)			
BMI[a]	5	0.36 (0.19, 0.54)	2.73	<.0001	0.01
Trunk-fat	6	0.61 (0.42, 0.80)	2.35	<.0001	0.00
Limb-fat[a]	10	0.44 (0.26, 0.63)	12.59	<.0001	33.21
Total body fat	2	0.02 (-0.49, 0.53)	0.13	0.93	0.00
Cholesterol	5	0.05 (-0.91, 1.10)	41.63	0.91	95.05
HDL[a]	4	0.42 (0.06, 0.78)	18.63	0.01	82.08
LDL	6	-0.14 (-0.87, 0.59)	74.65	0.70	92.91
TG	6	0.06 (-0.37, 0.49)	21.29	0.77	84.27

[a] Significant Outcomes

Table 11: Overall effect sizes (RE) and homogeneity assumptions for NNRTI combination category

Outcome	*k*	d (95% CI)	Homogeneity of effect sizes		I^2 (95% CI)
		Random-Effects	*Q*	*P-value*	
Weight	2	-0.01 (-0.57, 0.54)	21.72	0.95	95.40
BMI	5	0.23 (-0.11, 0.57)	28.89	0.18	83.50
Trunk-fat	2	0.46 (0.26, 0.67)	0.03	<.0001	0.00
Limb-fat	5	0.51 (0.34, 0.69)	1.90	<.0001	0.00
Total body fat					
Cholesterol[a]	3	1.09 (0.74, 1.43)	5.38	<.0001	66.18
HDL[a]	3	0.85 (0.54, 1.15)	4.92	<.0001	59.59
LDL	3	0.54 (0.37, 0.70)	1.32	<.0001	0.00
TG[a]	3	0.41 (0.10, 0.72)	6.18	0.008	70.28
SAT	N/A				
VAT	4	0.29 (0.12, 0.47)	2.02	0.0010	0.00
TAT	N/A				

[a] Significant Outcomes

Table 12: Multilevel MA model results on different outcomes in different ART treatment levels

Outcome	k	B-coefficient (95% CI) ART treatment levels	χ^2 statistics (Q) p-value
Weight	12	NRTI alone: 0.02 (0.03,0.38) PI alone: 0.33 (0.17, 0.50) LPV/r comb: 0.43 (0.18, 0.68)	<0.0001
BMI	15	LPV/r comb: 0.94 (0.53, 1.34) PI comb: 0.62 (0.28, 0.97) NNRTI com: 0.02 (0.07, 0.9)	<0.0001
Trunk-fat	26	PI alone: 0.47 (0.30, 0.64) NNRTI comb: 0.85 (0.01, 1.69)	<0.0001
Limb-fat	27	PI alone: 0.27 (0.1145, 0.4397) NNRTI comb: 1.05 (0.21, 1.89)	<0.0001
Cholesterol	29	LPV/r comb: 0.92(0.29, 1.54) NNRTI comb: 1.65 (0.95, 2.35)	<0.0001
HDL	31	LPV/r comb: 0.90 (0.47, 1.32) PI comb: 0.56 (0.11, 1.01) NNRTI comb: 1.09 (0.69, 1.49)	<0.0001
LDL	34	NNRTI: -1.08 (-1.99, 0.18) LPV/r comb: 0.94 (0.41, 1.47) NNRTI comb: 0.93 (0.26, 1.61)	<0.0001
TG	34	NRTI alone: 3.57 (2.16, 4.98) NNRTI alone: 1.30 (0.79, 1.81) LPV/r comb: 1.002 (0.32, 1.68) PI comb: -1.83 (-2.75, -0.92) NNRTI comb: 1.28 (0.81, 1.76)	<0.0001

Table 13: Multilevel MA model results including moderator analysis

Moderator Variable	Outcome	*k*	*B*-coefficient (95%CI)	Homogeneity of effect sizes		I^2 (95% CI)
				Q-statistic	*P-value*	
Weeks	Weight	12	-0.002 (-0.008, 0.004)	19.84	0.002	55.63%
	BMI	15	0.002 (-0.003, 0.008)	32.22	<0.0001	46.28%
	Trunk fat	26	0.003 (-0.002, 0.008)	30.40	<0.0001	55.97%
	Limb-fat	27	0.003 (-0.004, 0.009)	32.99	<0.0001	58.35%
	Cholesterol	29	-0.002 (-0.007, 0.004)	37.42	<0.0001	77.58%
	HDL	31	-0.001 (-0.003, 0.0007)	88.54	<0.0001	46.03%
	LDL*	34	-0.004 (-0.007, -0.002)	17.50	<0.0001	72.46%
	TG	34	0.0006 (-0.002, 0.003)	22.86	0.0018	60.14%
Publication Year	Weight	12	-0.02 (-0.1, 0.06)	19.75	0.003	55.55%
	BMI	15	0.04 (-0.002, 0.07)	36.55	<0.0001	42.39%
	Trunk fat	26	-0.02 (-0.07, 0.03)	32.35	<0.0001	52.39%
	Limb-fat*	27	0.06 (0.006, 0.12)	41.51	<0.0001	53.57%
	Cholesterol	29	-0.07 (-0.15, 0.0007)	5077	<0.0001	71.00%
	HDL*	31	-0.06 (-0.01, -0.02)	103.76	<0.0001	39.50%
	LDL*	34	-0.005 (-0.007, -0.001)	21.90	0.0026	81.95%
	TG*	34	-0.07(-0.1, -0.02)	40.13	<0.0001	40.32%
Female	Weight	12	-0.003 (-0.04, 0.03)	19.48	0.003	55.50%
	BMI	..	..	..	..	..
	Trunk fat	26	-0.007 (-0.016, 0.0006)	46.22	<0.0001	41.27%
	Limb-fat	27	-0.0019 (-0.014, 0.01)	29.62	<0.0001	62.21%
	Cholesterol	29	0.0048 (-0.008, 0.02)	36.31	<0.0001	78.51%
	HDL*	31	-0.006 (-0.01, -0.001)	101.60	<0.0001	39.78%
	LDL*	34	-0.01 (-0.019, -0.005)	41.79	<0.0001	72.07%
	TG	34	0.0012 (-0.004, 0.006)	22.63	0.0020	60.57%

Average mean age	Weight	12	-0.04 (-0.58, 0.49)	19.48	0.003	55.50%
	BMI	15	0.03 (-0.04, 0.09)	32.54	<0.0001	45.13%
	Trunk fat	26	0.02 (-0.03, 0.08)	31.24	<0.0001	54.08%
	Limb-fat	27	0.04 (-0.007, 0.10)	42.06	<0.0001	50.53%
	Cholesterol*	29	-0.17 (-0.23, -0.10)	117.09	<0.0001	44.92%
	HDL	31	-0.03 (-0.06, 0.01)	84.20	<0.0001	50.30%
	LDL	34	0.001 (-0.06, 0.07)	21.87	0.0027	82.04%
	TG*	34	-0.07 (-0.11, -0.04)	47.43	<0.0001	40.19%
Prop of white	Weight	..	..	..	..	..
	BMI	15	-0.41 (-1.67, 0.84)	32.28	<0.0001	45.22%
	Trunk-fat*	26	0.64 (0.35, 0.92)	89.16	<0.0001	18.71%
	Limb-fat*	27	0.73 (0.24, 1.23)	56.86	<0.0001	41.35%
	Cholesterol*	29	0.50 (0.02, 0.97)	47.85	<0.0001	73.02%
	HDL	31	0.24 (-0.08, 0.57)	82.53	<0.0001	51.75%
	LDL	34	0.45 (-0.08, 1.0)	25.75	0.0006	80.70%
	TG*	34	0.40 (0.07, 0.74)	32.28	<0.0001	51.16%
MQ	Weight	12	0.07 (-0.17, 0.33)	19.87	0.002	56.59%
	BMI	15	0.081 (-0.10, 0.26)	32.26	<0.0001	46.61%
	Trunk-fat	26	0.003 (-0.002, 0.008)	30.40	<0.0001	55.97%
	Limb-fat*	27	0.18 (0.005, 0.36)	38.73	<0.0001	56.39%
	Cholesterol	29	-0.14 (-0.36, 0.06)	41.61	<0.0001	75.85%
	HDL	31	-0.11 (-0.24, 0.01)	86.68	<0.0001	49.35%
	LDL	34	-0.09 (-0.30, 0.12)	22.88	0.0018	81.83%
	TG	34	-0.07 (-0.22, 0.07)	23.05	0.0017	61.76%

Table 14: List of moderators with no significant results

Proportion of black population
Proportion of Latino/Hispanic population
Proportion of Asian population
Proportion of other population
Mean body fat%
Mean sub-cutaneous adipose tissue
Mean visceral adipose tissue
Mean total adipose tissue
Mean fasting blood glucose
Mean fasting insulin level
Mean CD4 cell counts
Mean RNA level
Proportion of population reported Homosexuality as HIV route of transmission
Proportion of population reported Heterosexuality as HIV route of transmission
Proportion of population reported to ART adherence
Proportion of population reported on toxicity
Type of intervention settings
Number of intervention and comparison groups used
Participants assigned in intervention and comparison groups
Number of patients switched due to adverse drug reaction

Table 15: List of moderators unable to analyze due to lack of study reports

Mean Height of population
Mean waist-hip ratio of population
Mean BMI Over Weight
Mean BMI for Obese class1, class2, class3
Mean mid arm area
Mean mid-thigh area
Mean Hgba1C %
Proportion of population reported on drug use as HIV route of transmission
Proportion of population reported on blood transfusion as HIV route of transmission
Proportion of population reported on asymptomatic conditions
Proportion of population reported on symptomatic conditions
Proportion of population having Hepatitis B
Proportion of population having hepatitis C
Number of facilitator/provider
ART dosage used
Proportion of population having diabetes
Proportion of population having high blood pressure
Proportion of population having smoking habit
Type of intervention settings
Number of intervention and comparison groups used
Participants assigned in intervention and comparison groups

APPENDIX

Appendix 1: Comprehensive Literature Search Strategy

Searches run July 6-7, 2015
Total 506 citations after removing duplicates.
To get your total # for the flow diagram, add the original results + the additional from revised search. Then subtract 2 duplicates.

PubMed Search
1940's to present
Results: 427

(HIV OR "HIV"[Mesh] OR "Acquired Immunodeficiency Syndrome"[Mesh]) AND (Overweight OR "Overweight"[Mesh] OR BMI OR "body mass" OR "Body Mass Index"[MeSH] OR "Waist Circumference"[MeSH] OR "Weight Gain"[Mesh] OR "weight gain" OR anthropometric[ti] OR obesity OR "Obesity"[Mesh] OR obese OR "abdominal fat" OR adiposity OR "body fat") AND (HAART OR "Antiretroviral Therapy, Highly Active"[Mesh] OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals" OR "Anti-Retroviral Agents"[Mesh]) AND ("quasi-experimental" OR RCT OR "randomized controlled trial"[pt] OR (clinical[tiab] AND trial[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial" [pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh]) AND Humans[mesh] NOT (pregnan* OR wasting OR "weight loss" OR Lipodystroph* OR fever OR hepatitis OR carcinogen* OR neoplasm* OR cancer OR cancers OR "chronic liver disease" OR "liver fibrosis" OR "fatty liver disease" OR atherosclerosis OR "urinary metabolites" OR "urinary abnormalities" OR "renal impairment" OR "renal dysfunction" OR "bone mineral density" OR "skeletal muscle toxicity" OR "muscular dystrophy" OR "skeletal muscle disease" OR anemia OR tuberculosis OR "neurological disorder" OR "neurocognitive impairment" OR "lung disease" OR "alveolar disease" OR "genetic disease" OR "genetic abnormalities" OR biomarkers OR markers OR smoking[ti] OR dyslipidemi*[ti] OR dyslipidaemi*[ti] OR hypertriglyceridaemi*[ti])

Revised September 8, 2015: 360 after removing citations from original search

(HIV OR "HIV"[Mesh] OR "Acquired Immunodeficiency Syndrome"[Mesh]) AND (Overweight OR "Overweight"[Mesh] OR BMI OR "body mass" OR "Body Mass Index"[MeSH] OR "Waist Circumference"[MeSH] OR "Weight Gain"[Mesh] OR "weight gain" OR anthropometric[ti] OR obesity OR "Obesity"[Mesh] OR obese OR "abdominal fat" OR adiposity OR "body fat" OR lipohypertrophy) AND (NNRTI OR PI OR "protease inhibitor" OR HAART OR "Antiretroviral Therapy, Highly Active"[Mesh] OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals" OR "Anti-Retroviral Agents"[Mesh]) AND ("quasi-experimental" OR RCT OR "randomized controlled trial"[pt] OR (clinical[tiab] AND trial[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial" [pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh]) AND Humans[mesh] NOT (pregnan* OR wasting OR "weight

loss" OR fever OR hepatitis OR carcinogen* OR neoplasm* OR cancer OR cancers OR "chronic liver disease" OR "liver fibrosis" OR "fatty liver disease" OR atherosclerosis OR "urinary metabolites" OR "urinary abnormalities" OR "renal impairment" OR "renal dysfunction" OR "bone mineral density" OR "skeletal muscle toxicity" OR "muscular dystrophy" OR "skeletal muscle disease" OR anemia OR tuberculosis OR "neurological disorder" OR "neurocognitive impairment" OR "lung disease" OR "alveolar disease" OR "genetic disease" OR "genetic abnormalities" OR biomarkers OR markers OR smoking[ti])

Scopus search:

1823 to Present.
Citations: 131.
Limits: Article

Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2 part 1: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat")
OR
Concept 2 part 2 (in article title): anthropometric

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals")

AND

Concept 4 part 1: ("quasi-experimental" OR RCT OR "clinical trial" OR random*)
OR
Concept 4 part 2: (clinical AND trial)

NOT

Concept 5 part 1: (pregnan* OR wasting OR "weight loss" OR Lipodystroph* OR fever OR hepatitis OR carcinogen* OR neoplasm* OR cancer OR cancers OR "chronic liver disease" OR "liver fibrosis" OR "fatty liver disease" OR atherosclerosis OR "urinary metabolites" OR "urinary abnormalities" OR "renal impairment" OR "renal dysfunction" OR "bone mineral density" OR "skeletal muscle toxicity" OR "muscular dystrophy" OR "skeletal muscle disease" OR anemia OR tuberculosis OR "neurological disorder" OR "neurocognitive

impairment" OR "lung disease" OR "alveolar disease" OR "genetic disease" OR "genetic abnormalities" OR biomarkers OR markers)
OR
Concept 5 part 2 (in article title): rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review OR smoking OR dyslipidemi* OR dyslipidaemi* OR hypertriglyceridaemi*

Revised search: after removing original: 16

Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2 part 1: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat" OR lipohypertrophy)
OR
Concept 2 part 2 (in article title): anthropometric

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals" OR NNRTI OR PI OR "protease inhibitor")

AND

Concept 4 part 1: ("quasi-experimental" OR RCT OR "clinical trial" OR random*)
OR
Concept 4 part 2: (clinical AND trial)

NOT

Concept 5 part 1: (pregnan* OR wasting OR "weight loss" OR Lipodystroph* OR fever OR hepatitis OR carcinogen* OR neoplasm* OR cancer OR cancers OR "chronic liver disease" OR "liver fibrosis" OR "fatty liver disease" OR atherosclerosis OR "urinary metabolites" OR "urinary abnormalities" OR "renal impairment" OR "renal dysfunction" OR "bone mineral density" OR "skeletal muscle toxicity" OR "muscular dystrophy" OR "skeletal muscle disease" OR anemia OR tuberculosis OR "neurological disorder" OR "neurocognitive impairment" OR "lung disease" OR "alveolar disease" OR "genetic disease" OR "genetic abnormalities" OR biomarkers OR markers)
OR
Concept 5 part 2 (in article title): rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR

editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review OR smoking

CINAHL:
1981 to Present.
Citations: 2
Limits: Research article, Human, Exclude MEDLINE records.

Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2 part 1: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat")
OR
Concept 2 part 2 (in article title): anthropometric

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals")

AND

Concept 4 part 1: ("quasi-experimental" OR RCT OR "clinical trial" OR random*)
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OR

Concept 5 part 2 (in article title): rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review OR smoking OR dyslipidemi* OR dyslipidaemi* OR hypertriglyceridaemi*

Revised search: 0 studies after removing the original.

Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2 part 1: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat" OR lipohypertrophy)

OR

Concept 2 part 2 (in article title): anthropometric

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals" OR NNRTI OR "protease inhibitor" OR PI)

AND

Concept 4 part 1: ("quasi-experimental" OR RCT OR "clinical trial" OR random*)

OR

Concept 4 part 2: (clinical AND trial)

NOT

Concept 5 part 1: (pregnan* OR wasting OR "weight loss" OR fever OR hepatitis OR carcinogen* OR neoplasm* OR cancer OR cancers OR "chronic liver disease" OR "liver fibrosis" OR "fatty liver disease" OR atherosclerosis OR "urinary metabolites" OR "urinary abnormalities" OR "renal impairment" OR "renal dysfunction" OR "bone mineral density" OR "skeletal muscle toxicity" OR "muscular dystrophy" OR "skeletal muscle disease" OR anemia OR tuberculosis OR "neurological disorder" OR "neurocognitive impairment" OR "lung disease" OR "alveolar disease" OR "genetic disease" OR "genetic abnormalities" OR biomarkers OR markers)

OR

Concept 5 part 2 (in article title): rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review OR smoking

PsycINFO

1872 to Present
Citations: 4
Limits: Human

Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2 part 1: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat")
OR
Concept 2 part 2 (in article title): anthropometric

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals")

AND

Concept 4 part 1: ("quasi-experimental" OR RCT OR "clinical trial" OR random*)
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Concept 5 part 2 (in article title): rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review OR smoking OR dyslipidemi* OR dyslipidaemi* OR hypertriglyceridaemi*

Revised search: 0 after removing the original studies.

Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2 part 1: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat" OR lipohypertrophy)
OR
Concept 2 part 2 (in article title): anthropometric

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals" OR NNRTI OR "protease inhibitor" OR PI)

AND

Concept 4 part 1: ("quasi-experimental" OR RCT OR "clinical trial" OR random*)
OR
Concept 4 part 2: (clinical AND trial)

NOT

Concept 5 part 1: (pregnan* OR wasting OR "weight loss" OR fever OR hepatitis OR carcinogen* OR neoplasm* OR cancer OR cancers OR "chronic liver disease" OR "liver fibrosis" OR "fatty liver disease" OR atherosclerosis OR "urinary metabolites" OR "urinary abnormalities" OR "renal impairment" OR "renal dysfunction" OR "bone mineral density" OR "skeletal muscle toxicity" OR "muscular dystrophy" OR "skeletal muscle disease" OR anemia OR tuberculosis OR "neurological disorder" OR "neurocognitive impairment" OR "lung disease" OR "alveolar disease" OR "genetic disease" OR "genetic abnormalities" OR biomarkers OR markers)
OR
Concept 5 part 2 (in article title): rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "cross-sectional study" OR "case report" OR comment OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR "non-randomized" OR review OR smoking

Cochrane Library: 2 studies.
Current information only.
Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat" OR anthropometric)

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals")

NOT

Concept 4: (pregnan* OR wasting OR "weight loss" OR Lipodystroph* OR fever OR hepatitis OR carcinogen* OR neoplasm* OR cancer OR cancers OR "chronic liver disease" OR "liver fibrosis" OR "fatty liver disease" OR atherosclerosis OR "urinary metabolites" OR "urinary abnormalities" OR "renal impairment" OR "renal dysfunction" OR "bone mineral density" OR "skeletal muscle toxicity" OR "muscular dystrophy" OR "skeletal muscle disease" OR anemia OR tuberculosis OR "neurological disorder" OR "neurocognitive impairment" OR "lung disease" OR "alveolar disease" OR "genetic disease" OR "genetic abnormalities" OR biomarkers OR markers)

Revised search: 0 studies after removing the original studies.

Concept 1: (HIV OR "Acquired Immunodeficiency Syndrome")

AND

Concept 2: (Overweight OR BMI OR "body mass" OR "Waist Circumference" OR "weight gain" OR obesity OR obese OR "abdominal fat" OR adiposity OR "body fat" OR anthropometric OR lipohypertrophy)

AND

Concept 3: (HAART OR ART OR Antiretroviral* OR "Anti-retroviral" OR "Anti-retrovirals" OR NNRTI OR PI OR "protease inhibitor")

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Appendix 2: Data Extraction Coding Form

EFFECTS OF HIV-MEDICINES AMONG HIV POSITIVE PATIES ON BODY HABITUS CHANGE
A MULTILEVEL META-ANALYSIS

Developed August 30, 2015

Code ID: Nusrat=1, Ben=2, Dr. Huedo-medina=4

Study Information:
Study_ID: _____ (ID number 001, last name of First Author, Year of Publication without gaps)
Pub_YR: _____ (Publication Year)
Data_Coll_Yr: _____ (Year of data collection)
Lang: _____ (Language of report)
Journal: _____
Impact_Scr: _____ (Impact score of the journal; use ISI Web of Knowledge journal citation reports)
Fund_Srce: _____ (Funding Source) 0 = No funding 1 = Government 2 = Academic/University
3 = Private 4 = Both public and private
5 = Other Specific Funding grant: _____
Notes: _____

Region: _____ 0 = Not reported 1= United states 2 = Europe (city: _____)
3 = Central America/North America (Mexico, Canada, Caribbean city then specify: _____) 4 = Africa (city: _____)5 = Asia 6= Australia7 = Other/Multiple specify
(_____)

City_usa: _____ (USA only) **Zip_usa:** _____ (Zip-code; US only)

Demographic characteristics:				
mean±SD/Median (IQR) for age, gender and ethnicity provided by the study				
Characteristics	**IN1**	**IN2**	**IN3**	**IN4**
Age of participants Mean/median	Mean_age_IN1	Mean_age_IN2	Mean_age_IN3	Mean_age_IN4
SD of age	SD_age_IN1	SD_age_IN2	SD_age_IN3	SD_age_IN4
Number/proportion of female	Num/Prop_fem1	Num/Prop_fem2	Num/Prop_fem3	Num/Prop_fem4
Number/proportion of male	Num/Prop_male 1	Num/Prop_male2	Num/Prop_male 3	Num/Prop_male 4
Ethnicity if reported yes=1; no=0				
Number/ proportion of white	Prop_Whi	**Number/Proportion Black**	Prop_Bl	
Number/Proportion Latino/Hispanic	Prop_LH	**Number/Proportion Asian**	Prop_As	
Number/Proportion of Other/Mixed	Prop_oth			

Notes on sample characteristics relevant to coding

Anthropometric measurements in international units at baseline

Characteristic	IN1	IN2	IN3	IN4
Mean height (cm)	Mean_ht_IN1	Mean_htIN2	Mean_htIN3	Mean_htIN4
SD of height	Ht_SD_IN1	Ht_SD_IN2	Ht_SD_IN3	Ht_SD_IN4
Mean weight (kg)	Mean_wt_total	Mean_wt_IN1	Mean_wt_IN2	Mean_wt_IN3
SD of weight	Wt_SD_IN1	Wt_SD_IN2	Wt_SD_IN3	Wt_SD_IN4
Mean BMI (kg/m^2)	Mean_BMI_total	Mean_BMI_IN1	Mean_BMI_IN2	Mean_BMI_IN3
SD of BMI	SD_BMI_IN1	SD_BMI_IN2	SD_BMI_IN3	SD_BMI_IN4
Mean Waist circumference(cm)	Mean_WC_IN1	Mean_WC_IN2	Mean_WC_IN3	Mean_WC_IN4
SD of Waist circumference	SD_WC_IN1	SD_WC_IN2	SD_WC_IN3	SD_WC_IN4
Mean Waist-hip ratio	Mean_WHR_IN1	Mean_WHR_IN2	Mean_WHR_IN3	Mean_WHR_IN4
SD of Waist-hip ratio	SD_WHR_IN1	SD__WHR_IN2	SD_WHR_IN3	SD_WHR_IN4
BMI-Over-Weight	BMI_over_IN1	BMI_over_IN2	BMI_over_IN4	BMI_over_IN4
BMI-Obese-Class1	Obese1_IN1	Obese1_IN2	Obese1_IN3	Obese1_IN4
BMI-Obese-Class2	Obese2_IN1	Obese2_IN2	Obese2_IN3	Obese2_IN4
BMI-Obese-Class3	Obese3_IN1	Obese3_IN2	Obese3_IN3	Obese3_IN4
Mean body fat %	Mean_bodyfat_IN1	Mean_bodyfat_IN2	Mean_bodyfat_IN3	Mean_bodyfat_IN 4
SD of body fat %	SD_ bodyfat_IN1	SD_ bodyfat_IN2	SD_ bodyfat_IN3	SD_ bodyfat_IN4
Method of body fat % assessment				
Mean Trunk Fat %	Trunkfat_IN1	Trunkfat_IN2	Trunkfat_IN3	Trunkfat_IN4
Mean Limb Fat %	Limbfat_IN1	Limbfat_IN2	Limbfat_IN3	Limbfat_IN4
Mean Sub-cuteneous Adipose Tissue area (cm^2)	Mean_SAT_IN1	Mean_SAT_IN2	Mean_SAT_IN3	Mean_SAT_IN4
SD Sub-cutaneous Adipose Tissue area(cm^2)	SD_SAT_IN1	SD_SAT_IN2	SD_SAT_IN3	SD_SAT_IN4
Mean Visceral Adipose Tissue area (cm^2)	Mean_VAT_total	Mean_VAT_IN1	Mean_VAT_IN2	Mean_VAT_IN3
SD Visceral Adipose Tissue area (cm^2)	SD_VAT_IN1	SD_VAT_IN2	SD_VAT_IN3	SD_VAT_IN4
Mean Total Adipose Tissue Area (cm^2)				
SD Total Adipose Tissue Area (cm^2)				
Mean mid arm area				
SD of mid arm area				
Mean mid-thigh area				
SD of mid-thigh area				

Metabolic parameter, HIV risk assessment at baseline (Mean ±SD)

Characteristic	IN1	IN2	IN3	IN4
Mean fasting Blood Glucose (mmol/L)	Mean_fbloodglu_IN1	Mean_fbloodglu_IN2	Mean_fbloodglu_IN3	Mean_fbloodglu_IN4
SD of Fasting Blood glucose	SD_bdglu_IN1	SD_bdglu_IN2	SD_bdglu_IN3	SD_bdglu_IN4
Mean fasting Insulin (mclU/mL)	Mean_finsul_IN1	Mean_finsul_IN2	Mean_finsul_IN3	Mean_finsul_IN4
SD of fasting insulin	SD of finsul_IN1	SD of finsul_IN2	SD of finsul_IN3	SD of finsul_IN4
Mean HgbA1C as %	Mean_hgba1c_IN1	Mean_hgba1c_IN2	Mean_hgba1c_IN3	Mean_hgba1c_IN4
SD of HbA1C	SD_hgba1c_IN1	SD_hgba1c_IN2	SD_hgba1c_IN3	SD_hgba1c_IN4
Mean CD4 cell counts (cells/mm^3)	Mean_cd4_IN1	Mean_cd4_IN2	Mean_cd4_IN3	Mean_cd4_IN4
SD of CD4 cell counts (cells/mm^3)	SD_cd4_IN1	SD_cd4_IN2	SD_cd4_IN3	SD_cd4_IN4
Mean RNA level (log_{10} copies/mL)	Mean_rna_IN1	Mean_rna_IN2	Mean_rna_IN3	Mean_rna_IN4
SD of RNA level (log_{10} copies/mL)	SD_rna_IN1	SD_rna_IN2	SD_rna_IN3	SD_rna_IN4

Lipid profile at baseline (Mean ±SD)

Characteristic	IN1	IN2	IN3	IN4
Mean Cholesterol (mmol/l)	Mean_chol_IN1	Mean_chol_IN2	Mean_chol_IN3	Mean_chol_IN4
SD of Cholesterol	SD_chol_IN1	SD_chol_IN2	SD_chol_IN3	SD_chol_IN4
Mean LDL Cholesterol (mmol/l)	Mean_ldl_IN1	Mean_ldl_IN2	Mean_ldl_IN3	Mean_ldl_IN4
SD of LDL Cholesterol	SD_ ldl_IN1	SD_ ldl_IN2	SD_ ldl_IN3	SD_ ldl_IN4
Mean HDL Cholesterol (mmol/l)	Mean_hdl_IN1	Mean_hdl_IN1	Mean_hdl_IN2	Mean_hdl_IN3
SD of HDL Cholesterol	SD_hdl_IN1	SD_hdl_IN2	SD_hdl_IN3	SD_hdl_IN4
Mean Triglyceride (mmol/l)	Mean_tg_IN1	Mean_tg_IN2	Mean_tg_IN3	Mean_tg_IN4
SD of Triglyceride	SD_ tg_IN1	SD_ tg_IN2	SD_tg_IN3	SD_tg_IN4

Proportion of population on different characteristics				
HIV route of transmission reported: No=0, Yes=1				
Intervention/Comparison groups				
	IN1	**IN2**	**IN3**	**IN4**
Homosexual	Homo_IN1	Homo_IN2	Homo_IN3	Homo_IN4
Heterosexual	Hetero_IN1	Hetero_IN2	Hetero_IN3	Hetero_IN4
Drug users	Druguser_IN1	Druguser_IN2	Druguser_IN3	Druguser_IN4
Blood Transmission	Bldtran_IN1	Bldtran_IN2	Bldtran_IN3	Bldtran_IN4
Other				

Proportion of population on different characteristics in HIV diagnosis at baseline				
Characteristics	**IN1**	**IN2**	**IN3**	**IN4**
Prior to AIDS No=0, Yes=1, Unknown=2				
AIDS(CDCstage3)	AIDS_IN1	AIDS_IN2	AIDS_IN3	AIDS_IN4
Symptomatic(CDCstage2)	Symp_IN1	Symp_IN2	Symp_IN3	Symp_IN4
Asymptomatic(CDCstage1)	Asymp_IN1	Asymp_IN2	Asymp_IN3	Asymp_IN4
Hepatitis B virus	HebB_IN1	HepB_IN2	HepB_IN3	HepB_IN4
Hepatitis C virus	HebC_IN1	HepC_IN2	HepC_IN3	HepC_IN4

Intervention /Comparison Condition:				
Number of Participants in intervention and comparison groups in different events				
Intervention/Comparison groups				
	IN1	**IN2**	**IN3**	**IN4**
Participants at the beginning	Part_begIN1	Part_IN2	Part_IN3	Part_IN4
Participants at the end	Part_end_IN1	Part_end_IN2	Part_end_IN3	Part_end_IN4
Lost Follow Up/missing visits	Lost_fu			
Total number of F/U	Num_fu			
Participants withdraw after randomization/ withdraw consent	Withdraw			
Number of participants discontinued	Partc_discont			
Total participant adherence in %	%adherence			
Other reason for missing participants	Other_reasn			
Total number of deaths	Num_death			
Toxicity If reported yes=1; no=0	Toxic_rep			
Type of toxicity: Specify_____ (ex: hepatic toxicity, rash due to ART medication	Type_toxic			
Total number of participants having toxic effect	Part_toxic_effect			

Intervention and comparison conditions

Specify name of intervention conditions (ex: if specific drug of NRTI is given in the study write the name in full or short form):_____ IN_con_1; IN_con_2; IN_con_3; IN_con4; IN_con_5.

Intervention settings :_____ IN_setting
Categories:_____0= not reported 3= Hospital settings
1= private office 4= Multi-center: specify_____
2= HIV clinic/ center 5= Other: specify_____

Number of intervention and comparison groups used: _____ IN_com_groups
Categories:_____1= one control/comparison + one experimental group
2= one control/comparison + two experimental groups
3= one control/ comparison + three experimental groups
4= one control/ comparison + four experimental groups
Participants assignment in both conditions:_____ Assign_IN Assign_com
Categories: _____0= non-random assignment of individuals.
1= random assignment of individuals.
2= not clear/other: specify_____

Composition of both conditions:_____ Comp_IN Comp_com
Categories:_____0= targeted to individual (e.g. randomized as individual)
1= targeted to groups, other specify:_____
2= unclear

Number of participants switch from intervention conditions to comparison /control conditions due to drug reaction:
Numb_switch

Duration of intervention period: Specify in days, weeks, months.
Period_IN

Total number of facilitators in the study:_____ Numb_facil

Method of delivery: method_del
Categories: _____ 0= delivery by a nurse
1= delivery by a primary care provider
2= Delivery by a medical physician
3= Multiple/ other, specify: _____
4= Unclear

Dose in intervention and comparison conditions:___ dose_report
0= not reported; 1= yes reported

Amount of dose in intervention and comparison conditions: If unit varies, write unit within bracket.

	IN1_dose	IN2_dose	IN3_dose	IN4_dose

Length of follow up write specifically in days, weeks, months and years.

Length of follow up in different conditions	IN1_fu	IN2_fu	IN3_fu	IN4_fu

Risk Characteristics

Characteristic	IN1	IN2	IN3	IN4
Diabetes reported (1= yes, 0=no) If unreported == "."	diab_report			
Diabetes in proportions	Diab_IN1	Prop_Diab_IN2	Prop_Diab_IN3	Prop_Diab_IN4
BP reported (1=yes, 0=no)	bp_report			
Proportion having High blood pressure	BP_IN1	Prop_BP_IN2	Prop_BP_IN3	Prop_BP_IN4
LIFESTYLE VARIABLES				
Smokers/smokers (≤6 months) (0=no, 1=yes; if missing = ".")	Smoking_report			
Proportion of smoker	PROP_SMOKE_IN1	PROP_SMOKE_IN2	PROP_SMOKE_IN3	PROP_SMOKE_IN4

Notes on risk characteristics relevant to coding _____

Methodological Quality Control

MQ1____ Random assignment
0 =Violated randomization and/or nonequivalence of comparison group was not addressed
1 = Quasi-experimental design; arbitrary assignment; sequential; how:
_____
2 = Random assignment of groups of individuals. What unit:
_____
3 = Matching individuals on some variable What variable/s:
_____
4 = True randomization (i.e., participants had equal chance of receiving intervention)

MQ2____ Quality control 0 = No standardization of treatment is specified
1 = Treatment standardized by manual, specific training, content coding, video as main intervention strategy, etc

MQ3____ Pretest post-test design (at least one measure pre-post)? (0 = No, 1 = Yes)

MQ4____ Follow-up rate (i.e., largest FU rate at any delayed post-test, overall)
2 = 85-100% completed 1 = 70 – 84% completed 0 = <70%

MQ5____ Follow-up length (i.e., final assessment interval)

MQ10____ Withdrawal/Drop-outs (**This category applies to cases that withdrew after randomization)
0 = Not reported or all non-completers were excluded from analyses
1 = Enumerated and/or compared with completed cases (e.g., intent-to-treat; baseline differences)

MQ11____Attrition (**This category applies to cases lost to follow-up after treatment) 0 = Cases lost to follow-up are not considered in outcome reporting
1 = Enumerated and considered in outcome reporting (e.g., included in all possible analyses, imputed the mean for lost cases, compared with non-attrition at baseline)

MQ12____ Independent/Double-blinding
0 = Follow-up non-blind, unspecified, or questionnaire only
1 = Follow-up assessment completed by independent interviewer blind to group assgn

MQ13____Analyses
0 = No inferential statistical analysis; inappropriate, or unspecified
1 = Appropriate statistical analyses of group or time points differences (e.g., comparing two groups/measures using at least a t or F test but did not control for other characteristics). Code this category as well if they mention that groups were

2 = 6 months or longer 1 = > 3 months or < 6 months 0 = less than 3 months MQ6_____ Anonymity attempted (if face-to-face interviews, mark as '0') (0 = No/NR, 1 = Yes) MQ7_____ Low reactivity of measure completion (If they do not mention, code ".") 0 = no, intervention and measurement staff same and face-to-face interviews used 1 = yes, used different personnel for intervention and measurement (face-to-face) or measurement technique not highly reactive (written rather than oral questions, even if given by same person as intervention) MQ8_____ Collateral verification of self-report 0 = No collateral verification, not reported 1 = At least some collaterals interviewed; if known, _____%	comparable but do not report any statistical information about them at baseline or they do not mention any statistical test they used to demonstrate they did it.(i.e. test to compare group at FUP) 2 = Controlled for baseline and/or other characteristics in appropriate statistical analyses of group differences (e.g., compared two groups using at least a t or F test) (i.e. test to compare groups at FUP that controls for baseline, or no baseline differences found through test and thus no need to control for post comparison) MQ14_____Pilot testing 0 = None previous pilot testing of the intervention. 1 = There was a previous pilot testing of the intervention. MQ15_____Intervention content matched to sample (0 = No/NR, 1 = Yes) MQ16_____Incentives Offered (0 = No, 1 = Yes) MQ17_____Total Methodological Quality Score (out of 22 pts)
MQ9_____ Used objective measures (at FUP, not just baseline or for inclusion criteria) 0 = No objective measure used or unspecified (i.e., self-report only) 1 = Objective measures used in more than 50% of the cases	

List of HIV drugs:
NRTI drugs in combination: Specify subtype of NRTI
NNRTI drugs in combination: Specify subtype NNRTI
Protease inhibitors: Specify subtype pi
Combination of HIV medicines: Specify combination subtype comb

Study Quality (Cochrane Risk of Bias Table) on following characteristics:

Low risk of bias =Yes=1,High risk of bias =No=0,If not specific or, unclear=2

1. Random sequence generation
2. Allocation sequence concealment
3. Blinding of participants
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other bias

Appendix 3: Main HIV medicines with subclasses

Main ART Drug	Combined subclass	Dummy code
Combined (type12)	Comb1 (as they contain LPV/r as combined treatment)	4
Combined (type1+type12)	Comb1 (as they contain LPV/r as combined treatment)	4
Combined HIV medicine type 12+ type 11	Comb1 (as they contain LPV/r as combined treatment)	4
Combined HIV medicine type 12+ NNRTI type 4	Comb1 (as they contain LPV/r as combined treatment)	4
NNRTI+PI/r	Comb2 (as they contain PI)	5
NRTI+PI/r	Comb2 (as they contain PI)	5
NNRTI+NRTI	Comb3 (as they contain NNRTI with NRTI)	6
NRTI (type 7&4)+ Combined HIV medicine **LPVr** (Type 14)	Comb1 (as they contain LPV/r as combined treatment)	4
NNRTI (type4)+Combined HIV medicine **LPV/r** (type 14)	Comb1 (as they contain LPV/r as combined treatment)	4
Combined (type12)	Comb1 (as they contain LPV/r as combined treatment)	4
Combined (type11+type 12)	Comb1 (as they contain LPV/r as combined treatment)	4
PI+NRTI(type 2+type4)	Comb2 (as they contain PI)	5
PI+NRTI(type 2+type5)	Comb2 (as they contain PI)	5
PI (type7)+NRTI(type2+type5)	Comb2 (as they contain PI)	5
NNRTI(Type 2)+Combination HIV medicine TDF/FTC (Type12)	Comb3 (as they contain NNRTI type2)	6
NNRTI(Type 2)+Combination HIV medicine ABC/3TC (Type1)	Comb3 (as they contain NNRTI type2)	6
PI+Combination HIV medicine TDF/FTC (Type12)	Comb2 (as they contain PI)	5
PI+Combination HIV medicine ABC/3TC (Type1)	Comb2 (as they contain PI)	5
NNRTI(Type 2)+Combination HIV medicine TDF/FTC (Type12)	Comb3 (as they contain NNRTI type2)	6
NNRTI(Type 2)+Combination HIV medicine ABC/3TC (Type1)	Comb3 (as they contain NNRTI type2)	6
PI+Combination HIV medicine TDF/FTC (Type12)	Comb2 (as they contain PI)	5
PI+Combination HIV medicine ABC/3TC (Type1)	Comb2 (as they contain PI)	5
NRTI (type 5+ Type 1)	NRTI	1
PI/NNRTI+NRTI(ABC Type1)	Comb2 (as they contain PI)	5
NRTI (Type5+ Type1 + Type 7)+PI/NNRTI	Comb2 (as they contain PI)	5
NRTI (type2+3)and NNRTI (type2)	Comb3 (as they contain NNRTI type2)	6
NRTI (type5&2) and NNRTI (type2)	Comb3 (as they contain NNRTI type2)	6
PI	PI	3
NNRTI	NNRTI	2
PI+NNRTI	Comb2 (as they contain PI)	5
NRTI	NRTI	1
NNRTI+PI	Comb2 (as they contain PI)	5
NRTI(Type4&7)+Combination HIV medicine LPV/r(Type14)	Comb1 (as they contain LPV/r as combined treatment)	4
NNRTI(Type 4)+Combination HIV medicine LPV/r(Type14)	Comb1 (as they contain LPV/r as combined treatment)	4

Appendix 4: R syntax

Run the Library in R

```
Library ("metafor")
```

#Overall effect sizes

#Regimen NRTI on outcome variable WEIGHT:

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==1),data=HIVdata,method="REML")

model1
```

#Regimen NRTI on outcome variable BMI:

```
model2<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==2),data=HIVdata,method="REML")

model2
```

#Regimen NRTI on outcome variable TRUNKFAT:

```
model3<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==3),data=HIVdata,method="REML")

model3
```

#Regimen NRTI on outcome variable LIMBFAT:

```
model4<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==4),data=HIVdata,method="REML")

model4
```

#Regimen NRTI on outcome variable TOTAL BODY FAT:

```
model5<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==5),data=HIVdata,method="REML")

model5
```

#Regimen NRTI on outcome variable CHOLESTEROL:

```
model6<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==6),data=HIVdata,method="REML")

model6
```

#Regimen NRTI on outcome variable HDL:

```
model7<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==7),data=HIVdata,method="REML")

model7
```

#Regimen NRTI on outcome variable LDL:

```
model8<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==8),data=HIVdata,method="REML")

mod
```

#Regimen NRTI on outcome variable TG:

```
model9<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==9),data=HIVdata,method="REML")

model9
```

#Regimen NRTI on outcome variable SAT:

```
model10<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==10),data=HIVdata,method="REML")

model10
```

#Regimen NRTI on outcome variable VAT:

```
model11<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==11),data=HIVdata,method="REML")

model11
```

#Regimen NRTI on outcome variable TAT:

```
model12<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==12),data=HIVdata,method="REML")

model12
```

#Regimen NNRTI on outcome variable WEIGHT:

###Special note:

#No studies reported data on WEIGHT, BMI, Trunkfat,Limbfat, Total bodyfat, SAT, VAT, TAT.Only provided on HDL, LDL, TG for NNRTI regimen.

#That is why we got error messages. Only one study reported those outcome variable that is why result showing Fixed effects instead of Random effect.

```
model13<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==1),data=HIVdata,method="REML")
```

```
model13
```

#Regimen NNRTI on outcome variable BMI:

```
model14<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==2),data=HIVdata,method="REML")

model14
```

#Regimen NNRTI on outcome variable TRUNKFAT:

```
model15<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==3),data=HIVdata,method="REML")

model15
```

#Regimen NNRTI on outcome variable LIMBFAT:

```
model16<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==4),data=HIVdata,method="REML")

model16
```

#Regimen NNRTI on outcome variable TOTAL BODY FAT:

```
model17<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==5),data=HIVdata,method="REML")

model17
```

#Regimen NNRTI on outcome variable CHOLESTEROL:

```
model18<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==6),data=HIVdata,method="REML")

model18
```

#Regimen NNRTI on outcome variable HDL:

```
model19<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==7),data=HIVdata,method="REML")

model19
```

#Regimen NNRTI on outcome variable LDL:

```
model20<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==8),data=HIVdata,method="REML")

model20
```

#Regimen NNRTI on outcome variable TG:

```
model21<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==9),data=HIVdata,method="REML")

model21
```

#Regimen NNRTI on outcome variable SAT:

```
model22<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==10),data=HIVdata,method="REML")

model22
```

#Regimen NNRTI on outcome variable VAT:

```
model23<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==11),data=HIVdata,method="REML")

model23
```

#Regimen NNRTI on outcome variable TAT:

```
model24<-
rma(d.ex.,var_d.ex.,subset=(trt==2&Outcome==12),data=HIVdata,method="REML")

model24
```

#Regimen PI on outcome variable WEIGHT:

```
model25<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==1),data=HIVdata,method="REML")

model25
```

#Regimen PI on outcome variable BMI:

No data on BMI for PI regimen. that is why we got error message.

```
model26<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==2),data=HIVdata,method="REML")

model26
```

#Regimen PI on outcome variable TRUNKFAT:

```
model27<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==3),data=HIVdata,method="REML")

model27
```

#Regimen PI on outcome variable LIMBFAT:

```
model28<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==4),data=HIVdata,method="REML")

model28
```

#Regimen PI on outcome variable TOTAL BODY FAT:

No data on TBF. That is why we got error messages.

```
model29<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==5),data=HIVdata,method="REML")

model29
```

#Regimen PI on outcome variable CHOLESTEROL:

```
model30<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==6),data=HIVdata,method="REML")

model30
```

#Regimen PI on outcome variable HDL:

```
model31<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==7),data=HIVdata,method="REML")

model31
```

#Regimen PI on outcome variable LDL:

```
model32<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==8),data=HIVdata,method="REML")

model32
```

#Regimen PI on outcome variable TG:

```
model33<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==9),data=HIVdata,method="REML")

model33
```

#Regimen PI on outcome variable SAT:

No data on SAT, VAT and TAT for PI regimen. That is why we got error messages.

```
model34<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==10),data=HIVdata,method="REML")

model34
```

#Regimen PI on outcome variable VAT:

```
model35<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==11),data=HIVdata,method="REML")

model35
```

#Regimen PI on outcome variable TAT:

```
model36<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==12),data=HIVdata,method="REML")

model36
```

#Regimen COMB1 on outcome variable WEIGHT:

```
model37<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==1),data=HIVdata,method="REML")

model37
```

#Regimen COMB1 on outcome variable BMI:

```
model38<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==2),data=HIVdata,method="REML")

model38
```

#Regimen COMB1 on outcome variable TRUNKFAT:

```
model39<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==3),data=HIVdata,method="REML")

model39
```

#Regimen COMB1 on outcome variable LIMBFAT:

```
model40<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==4),data=HIVdata,method="REML")

model40
```

#Regimen COMB1 on outcome variable TOTAL BODY FAT:

```
model41<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==5),data=HIVdata,method="REML")

model41
```

#Regimen COMB1 on outcome variable CHOLESTEROL:

```
model42<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==6),data=HIVdata,method="REML")

model42
```

#Regimen COMB1 on outcome variable HDL:

```
model43<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==7),data=HIVdata,method="REML")

model43
```

#Regimen COMB1 on outcome variable LDL:

```
model44<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==8),data=HIVdata,method="REML")

model44
```

#Regimen COMB1 on outcome variable TG:

```
model45<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),data=HIVdata,method="REML")

model45
```

#Regimen COMB1 on outcome variable SAT:

```
model46<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==10),data=HIVdata,method="REML")

model46
```

#Regimen COMB1 on outcome variable VAT:

```
model47<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==11),data=HIVdata,method="REML")

model47
```

#Regimen COMB1 on outcome variable TAT:

```
model48<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==12),data=HIVdata,method="REML")

model48
```

#Regimen COMB2 on outcome variable WEIGHT:

```
model49<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==1),data=HIVdata,method="REML")

model49
```

#Regimen COMB2 on outcome variable BMI:

```
model50<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==2),data=HIVdata,method="REML")

model50
```

#Regimen COMB2 on outcome variable TRUNKFAT:

No data on trunkfat,

```
model51<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==3),data=HIVdata,method="REML")

model51
```

#Regimen COMB2 on outcome variable LIMBFAT:

```
model53<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==4),data=HIVdata,method="REML")

model53
```

#Regimen COMB2 on outcome variable TOTAL BODY FAT:

```
model54<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==5),data=HIVdata,method="REML")

model54
```

#Regimen COMB2 on outcome variable CHOLESTEROL:

```
model55<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==6),data=HIVdata,method="REML")

model55
```

#Regimen COMB2 on outcome variable HDL:

```
model56<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==7),data=HIVdata,method="REML")

model56
```

#Regimen COMB2 on outcome variable LDL:

```
model57<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==8),data=HIVdata,method="REML")

model57
```

#Regimen COMB2 on outcome variable TG:

```
model58<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==9),data=HIVdata,method="REML")

model58
```

#Regimen COMB2 on outcome variable SAT:

No data on SAT.

```
model59<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==10),data=HIVdata,method="REML")

model59
```

#Regimen COMB2 on outcome variable VAT:

```
model60<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==11),data=HIVdata,method="REML")

model60
```

#Regimen COMB2 on outcome variable TAT:

```
model61<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==12),data=HIVdata,method="REML")

model61
```

#Regimen COMB3 on outcome variable WEIGHT:

```
model62<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==1),data=HIVdata,method="REML")

model62
```

#Regimen COMB3 on outcome variable BMI:

```
model63<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==2),data=HIVdata,method="REML")

model63
```

#Regimen COMB3 on outcome variable TRUNKFAT:

```
model64<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==3),data=HIVdata,method="REML")

model64
```

#Regimen COMB3 on outcome variable LIMBFAT:

```
model65<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==4),data=HIVdata,method="REML")

model65
```

#Regimen COMB3 on outcome variable TOTAL BODY FAT:

No data on TBF for COMB3 regimen

```
model66<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==5),data=HIVdata,method="REML")

model66
```

#Regimen COMB3 on outcome variable CHOLESTEROL:

```
model67<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==6),data=HIVdata,method="REML")

model67
```

#Regimen COMB3 on outcome variable HDL:

```
model68<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==7),data=HIVdata,method="REML")

model68
```

#Regimen COMB3 on outcome variable LDL:

```
model69<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==8),data=HIVdata,method="REML")
```

model69

#Regimen COMB3 on outcome variable TG:

```
model70<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==9),data=HIVdata,method="REML")

model70
```

#Regimen COMB3 on outcome variable SAT: No data on SAT.

```
model71<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==10),data=HIVdata,method="REML")

model71
```

#Regimen COMB3 on outcome variable VAT:

```
model72<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==11),data=HIVdata,method="REML")

model72
```

#Regimen COMB3 on outcome variable TAT:

No data on TAT.

```
model73<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==12),data=HIVdata,method="REML")

model73
```

R code for forest plot

NRTI for BMI

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==2),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))
model1
par("usr")
forest(model1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,5,"BMI")
text(c(-2,2),5,c("NRTI ","Baseline"))
text(-6,5,"Author Year",pos=4)
text(5,5,"d[95% CI]",pos=4)
par(op)
```

NRTI for cholesterol

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==6),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))
par("usr")
forest(model6,xlim=c(-5,6),xlab="Standardized Mean
Difference",cex=.9,efac=3,col="dark red",border="black")
op<-par(cex=0.98, font=2,col="black")
op<-par(cex=0.98, font=2,col="dark red")
text (0,13,"Cholesterol")
text(c(-2,2),13,c("Favors Baseline ","Favors Intervention"))
text(-5,13,"Author Year",pos=4)
text(4,13,"d[95% CI]",pos=4)
par(op)
```

NRTI for HDL

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==7),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))
par("usr")
forest(model14,xlim=c(-5,6),xlab="Standardized Mean
Difference",cex=.90,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.90, font=2,col="dark red")
text (0,14,"LDL")
text(c(-2,2),14,c("NRTI ","Baseline"))
text(-5,14,"Author Year",pos=4)
text(4,14,"d[95% CI]",pos=4)
par(op)
```

NRTI for LDL

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==8),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))
par("usr")
forest(model14,xlim=c(-5,6),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,15,"LDL")
text(c(-2,2),15,c("NRTI ","Baseline"))
text(-5,15,"Author Year",pos=4)
text(4,15,"d[95% CI]",pos=4)
par(op)
```

NRTI for TG

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==9),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))

par("usr")
forest(model14,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,15,"TG")
text(c(-2,2),15,c("NRTI ","Baseline"))
text(-6,15,"Author Year",pos=4)
text(7.5,15,"d[95% CI]",pos=4)
par(op)
```

NRTI for trunk fat

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==3),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))

par("usr")
forest(model1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,12,"Trunk Fat")
text(c(-2,2),12,c("Baseline","NRTI"))
text(-6,12,"Author Year",pos=4)
text(5,12,"d[95% CI]",pos=4)
par(op)
```

NRTI for limb fat

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==5),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))

par("usr")
forest(model1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,10,"Limb Fat")
text(c(-2,2),10,c("Baseline","NRTI"))
text(-6,10,"Author Year",pos=4)
text(5,10,"d[95% CI]",pos=4)
par(op)
```

NRTI for Total fat

```
model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==5),data=HIVdata,method="REML",
slab= paste(Author, Year, sep=""))
par("usr")
forest(model1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,14,"Total Fat")
text(c(-2,2),14,c("Baseline","NRTI"))
text(-6,14,"Author Year",pos=4)
```

```
text(5,14,"d[95% CI]",pos=4)
par(op)
```

PI for Weight

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==1),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
PI for Weight
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.4,"Weight")
text(c(-2,2),3.4,c("Baseline","PI"))
text(-6,3.4,"Author Year",pos=4)
text(5,3.4,"d[95% CI]",pos=4)
par(op)
```

PI for BMI

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==2),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.4,"BMI")
text(c(-2,2),3.4,c("Baseline","PI"))
text(-6,3.4,"Author Year",pos=4)
text(5,3.4,"d[95% CI]",pos=4)
par(op)
```

PI for Trunk fat

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==3),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
```

```
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.4,"Trunk Fat")
text(c(-2,2),3.4,c("Baseline","PI"))
text(-6,3.4,"Author Year",pos=4)
text(5,3.4,"d[95% CI]",pos=4)
par(op)par("usr")
forest(PI,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.4,"Trunk Fat")
text(c(-2,2),3.4,c("NRTI ","Baseline"))
text(-6,3.4,"Author Year",pos=4)
text(5,3.4,"d[95% CI]",pos=4)
par(op)
```

PI for Limb Fat

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==4),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.4,"Limb Fat")
text(c(-2,2),3.4,c("Baseline","PI"))
text(-6,3.4,"Author Year",pos=4)
text(5,3.4,"d[95% CI]",pos=4)
par(op)
```

PI for Total Fat

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==5),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.4,"Total Fat")
text(c(-2,2),3.4,c("Baseline","PI"))
text(-6,3.4,"Author Year",pos=4)
```

```
text(5,3.4,"d[95% CI]",pos=4)
par(op)
PI for cholesterol
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==6),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.4,"Cholesterol")
text(c(-2,2),3.4,c("Baseline","PI"))
text(-6,3.4,"Author Year",pos=4)
text(5,3.4,"d[95% CI]",pos=4)
par(op)
```

PI for HDL

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==7),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,5,"HDL")
text(c(-2,2),5,c("Baseline","PI"))
text(-6,5,"Author Year",pos=4)
text(5,5,"d[95% CI]",pos=4)
par(op)
```

PI for LDL

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==8),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,5,"LDL")
text(c(-2,2),5,c("Baseline","PI"))
```

```
text(-6,5,"Author Year",pos=4)
text(5,5,"d[95% CI]",pos=4)
par(op)
```

PI for TG

```
pi<-
rma(d.ex.,var_d.ex.,subset=(trt==3&Outcome==9),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
pi
par("usr")
forest(pi,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,5,"TG")
text(c(-2,2),5,c("Baseline","PI"))
text(-6,5,"Author Year",pos=4)
text(5,5,"d[95% CI]",pos=4)
par(op)
```

COMB1 for WEIGHT

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==1),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,6,"WEIGHT")
text(c(-2,2),6,c("Baseline","PI"))
text(-6,6,"Author Year",pos=4)
text(5,6,"d[95% CI]",pos=4)
par(op)
```

COMB1 for BMI

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==2),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
```

```
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.5,"BMI")
text(c(-2,2),3.5,c("Baseline","PI"))
text(-6,3.5,"Author Year",pos=4)
text(5,3.5,"d[95% CI]",pos=4)
par(op)
```

COMB1 for TRUNK FAT

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==3),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,9.5,"TRUNK FAT")
text(c(-2,2),9.5,c("Baseline",”COMB ART"))
text(-6,9.5,"Author Year",pos=4)
text(5,9.5,"d[95% CI]",pos=4)
par(op)
```

COMB1 for LIMB FAT

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==4),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,6,"LIMB FAT")
text(c(-2,2),6,c("Baseline","COMB ART"))
text(-6,6,"Author Year",pos=4)
text(5,6,"d[95% CI]",pos=4)
par(op)
```

COMB1 for TOTAL FAT

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==5),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
```

```
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,8,"TOTAL FAT")
text(c(-2,2),8,c("Baseline","COMB ART"))
text(-6,8,"Author Year",pos=4)
text(5,8,"d[95% CI]",pos=4)
par(op)
```

COMB1 for CHOLETEROL

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==6),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,10,"Cholesterol")
text(c(-2,2),10,c("Baseline","COMB ART"))
text(-6,10,"Author Year",pos=4)
text(5,10,"d[95% CI]",pos=4)
par(op)
```

COMB1 for HDL

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==7),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,10,"HDL")
text(c(-2,2),10,c("Baseline","COMB ART"))
text(-6,10,"Author Year",pos=4)
text(5,10,"d[95% CI]",pos=4)
par(op)
```

COMB1 for LDL

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==8),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,10,"LDL")
text(c(-2,2),10,c("Baseline","COMB ART"))
text(-6,10,"Author Year",pos=4)
text(5,10,"d[95% CI]",pos=4)
par(op)
```

COMB1 for tg

```
COMB1<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB1
par("usr")
forest(COMB1,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,10,"TG")
text(c(-2,2),10,c("Baseline","COMB ART"))
text(-6,10,"Author Year",pos=4)
text(5,10,"d[95% CI]",pos=4)
par(op)
```

COMB2 for Weight

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==1),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2
par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3,"Weight")
text(c(-2,2),3,c("Baseline","COMB2 ART"))
text(-6,3,"Author Year",pos=4)
text(5,3,"d[95% CI]",pos=4)
```

```
par(op)
```

COMB2 for BMI

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==2),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2

par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,7,"BMI93 | P a g e ")
text(c(-2,2),7,c("Baseline","COMB2 ART"))
text(-6,7,"Author Year",pos=4)
text(5,7,"d[95% CI]",pos=4)
par(op)
```

COMB2 for Trunk fat

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==3),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2

par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,8,"TRUNK FAT")
text(c(-2,2),8,c("Baseline","COMB2 ART"))
text(-6,8,"Author Year",pos=4)
text(5,8,"d[95% CI]",pos=4)
par(op)
```

COMB2 for Limb fat

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==4),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2
par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
```

```
op<-par(cex=0.85, font=2,col="dark red")
text (0,12,"LIMB FAT")
text(c(-2,2),12,c("Baseline","COMB2 ART"))
text(-6,12,"Author Year",pos=4)
text(5,12,"d[95% CI]",pos=4)
par(op)
```

COMB2 for Total fat

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==5),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2
par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.5,"TOTAL FAT")
text(c(-2,2),3.5,c("Baseline","COMB2 ART"))
text(-6,3.5,"Author Year",pos=4)
text(5,3.5,"d[95% CI]",pos=4)
par(op)
```

COMB2 for cholesterol

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==6),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2

par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,6.5,"Cholesterol")
text(c(-2,2),6.5,c("Baseline","COMB2 ART"))
text(-6,6.5,"Author Year",pos=4)
text(5,6.5,"d[95% CI]",pos=4)
par(op)
```

COMB2 for HDL

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==7),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
```

```
COMB2
par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,6,"HDL")
text(c(-2,2),6,c("Baseline","COMB2 ART"))
text(-6,6,"Author Year",pos=4)
text(5,6,"d[95% CI]",pos=4)
par(op)
```

COMB2 for LDL

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==8),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2
par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,7.5,"LDL")
text(c(-2,2),7.5,c("Baseline","COMB2 ART"))
text(-6,7.5,"Author Year",pos=4)
text(5,7.5,"d[95% CI]",pos=4)
par(op)
```

COMB2 for TG

```
COMB2<-
rma(d.ex.,var_d.ex.,subset=(trt==5&Outcome==9),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB2
par(op)par("usr")
forest(COMB2,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,7.5,"TG")
text(c(-2,2),7.5,c("Baseline","COMB2 ART"))
text(-6,7.5,"Author Year",pos=4)
text(5,7.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for weight

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==1),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3


par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.5,"Weight")
text(c(-2,2),3.5,c("Baseline","COMB3 ART"))
text(-6,3.5,"Author Year",pos=4)
text(5,3.5,"d[95% CI]",pos=4)
par(op)
```

Comb 3 for BMI

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==2),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3

par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,7.5,"BMI")
text(c(-2,2),7.5,c("Baseline","COMB3 ART"))
text(-6,7.5,"Author Year",pos=4)
text(5,7.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for Trunk

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==3),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3
par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,3.5,"TRUNK FAT")
text(c(-2,2),3.5,c("Baseline","COMB3 ART"))
```

```
text(-6,3.5,"Author Year",pos=4)
text(5,3.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for LIMB

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==4),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3
par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,7.5,"LIMB FAT")
text(c(-2,2),7.5,c("Baseline","COMB3 ART"))
text(-6,7.5,"Author Year",pos=4)
text(5,7.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for Total fat

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==5),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3
par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,7.5,"Total FAT")
text(c(-2,2),7.5,c("Baseline","COMB3 ART"))
text(-6,7.5,"Author Year",pos=4)
text(5,7.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for Cholesterol

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==6),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3
par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
```

```
text (0,4.5,"Cholesterol")
text(c(-2,2),4.5,c("Baseline","COMB3 ART"))
text(-6,4.5,"Author Year",pos=4)
text(5,4.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for HDL

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==7),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3


par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,4.5,"HDL")
text(c(-2,2),4.5,c("Baseline","COMB3 ART"))
text(-6,4.5,"Author Year",pos=4)
text(5,4.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for LDL

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==8),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3


par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,4.5,"LDL")
text(c(-2,2),4.5,c("Baseline","COMB3 ART"))
text(-6,4.5,"Author Year",pos=4)
text(5,4.5,"d[95% CI]",pos=4)
par(op)
```

COMB3 for TG

```
COMB3<-
rma(d.ex.,var_d.ex.,subset=(trt==6&Outcome==9),data=HIVdata,method="REML",sl
ab= paste(Author,Year,sep=""))
COMB3
par(op)par("usr")
forest(COMB3,xlim=c(-6,7),xlab="Standardized Mean
Difference",cex=.85,efac=2,col="dark red",border="black")
op<-par(cex=0.85, font=2,col="black")
op<-par(cex=0.85, font=2,col="dark red")
text (0,4.5,"TG")
text(c(-2,2),4.5,c("Baseline","COMB3 ART"))
text(-6,4.5,"Author Year",pos=4)
text(5,4.5,"d[95% CI]",pos=4)
par(op)
```

R syntax for Meta regression plot

```
model100<-rma(d.ex.,var_d.ex.,subset=(trt==1 & Outcome==8),mods=Weeks,dat
a=HIVdata, method="REML",slab= paste(Reference, Pub_Year, sep =","))
model100pred <- predict(model100,newmods=cbind(seq(0,208,.1)))
wi=HIVdata$w_d.ex.
min= min(wi,na.rm=TRUE)
max= max(wi,na.rm=TRUE)
size= 1.0 + 6.0 * (wi - min)/(max - min)
treatldl= subset(HIVdata,trt==1 & Outcome==8)

#Here we have to create the subsample we are working on to just plot the observed
values of that below
plot(treatldl$Weeks,treatldl$d.ex.,pch= 21,col="black",bg ="white",cex=size,xlab=
"Number of Weeks",

#Plotting here the observed values of the subsample
ylab = "LDL Effect Size (d)",xlim=c(0,260),ylim=c(-1,1 ))
lines(seq(0,208,.1), model100pred$pred,col = "dark red")

#Plotting here the regression line and confidence interval of the predictive model
lines(seq(0,208,.1), model100pred$ci.lb,lty = "dashed", col="dark red")
lines(seq(0,208,.1), model100pred$ci.ub,lty = "dashed", col="dark red")
model100<-rma(d.ex.,var_d.ex.,subset=(trt==1 & Outcome==8),mods=Weeks,dat
a=HIVdata,method="REML",slab= paste(Reference,Pub_Year,sep =","))
model100pred <- predict(model100, newmods=cbind(seq(0,208,.1)))
model100
```

R SYNTAX FOR MODERATOR ANALYSIS Risk of Bias:

```
rsg<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),mods=~factor(rand_sequence),da
ta=HIVdata,method="REML")

rsg

alloc<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),mods=~factor(alloc_conc),data=H
IVdata,method="REML")

alloc

blind<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),mods=~factor(blinding),data=HI
Vdata,method="REML")

blind

outblind<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),mods=~factor(outcome_blind),da
ta=HIVdata,method="REML")

outblind

incomp<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),mods=~factor(incompl_outc_data
),data=HIVdata,method="REML")

incomp

selectreport<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==9),mods=~factor(select_report),data
=HIVdata,method="REML")

selectreport

otherbias<-
rma(d.ex.,var_d.ex.,subset=(trt==4&Outcome==1),mods=~factor(other_bias),data=
HIVdata,method="REML")

library("metafor")


#Regimen NRTI on outcome variable WEIGHT:

model1<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==1),data=HIVdata,method="REML")

model1
```

```
Publication Bias

#pub bias for NRTI and Weight

#Egger's

regtest(model1,model="lm",data=HIVdata)

#Begg's

ranktest(model1, data=HIVdata)

#funnel plot

model1trim=trimfill(model1,data=HIVdata)

funnel(model1trim)


#Regimen NRTI on outcome variable BMI:

model2<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==2),data=HIVdata,method="REML")

model2

Publication Bias

#pub bias for NRTI and BMI

#Egger's

regtest(model2,model="lm",data=HIVdata)

#Begg's

ranktest(model2,data=HIVdata)

#funnel plot

model2trim=trimfill(model2,data=HIVdata)

funnel(model2trim)


#Regimen NRTI on outcome variable TRUNKFAT:

model3<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==3),data=HIVdata,method="REML")

model3

Publication Bias
```

```
#pub bias for NRTI and BMI
#Egger's
regtest(model3,model="lm",data=HIVdata)
#Begg's
ranktest(model3,data=HIVdata)
#funnel plot
model3trim=trimfill(model3,data=HIVdata)
funnel(model3trim)

#Regimen NRTI on outcome variable LIMBFAT:
model4<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==4),data=HIVdata,method="REML")
model4
Publication Bias
#pub bias for NRTI and LIMBFAT
#Egger's
regtest(model4,model="lm",data=HIVdata)
#Begg's
ranktest(model4,data=HIVdata)
#funnel plot
model4trim=trimfill(model4,data=HIVdata)
funnel(model4trim)

#Regimen NRTI on outcome variable TOTAL BODY FAT:
model5<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==5),data=HIVdata,method="REML")
model5
Publication Bias
#pub bias for NRTI and TOTAL BODY FAT:
```

```
#Egger's
regtest(model5,model="lm",data=HIVdata)
#Begg's
ranktest(model5,data=HIVdata)
#funnel plot
model5trim=trimfill(model5,data=HIVdata)
funnel(model5trim)
#Regimen NRTI on outcome variable CHOLESTEROL:
model6<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==6),data=HIVdata,method="REML")
model6
```

Publication Bias

#pub bias for NRTI and CHOLESTEROL:

```
#Egger's
regtest(model6,model="lm",data=HIVdata)
#Begg's
ranktest(model6,data=HIVdata)
#funnel plot
model6trim=trimfill(model6,data=HIVdata)
funnel(model6trim)

#Regimen NRTI on outcome variable HDL:
model7<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==7),data=HIVdata,method="REML")
model7
```

Publication Bias

#pub bias for NRTI and HDL:

```
#Egger's
```

```
regtest(model7,model="lm",data=HIVdata)
#Begg's
ranktest(model7,data=HIVdata)
#funnel plot
model7trim=trimfill(model7,data=HIVdata)
funnel(model7trim)

#Regimen NRTI on outcome variable LDL:
model8<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==8),data=HIVdata,method="REML")
model8
#pub bias for NRTI and LDL:
#Egger's
regtest(model8,model="lm",data=HIVdata)
#Begg's
ranktest(model8,data=HIVdata)
#funnel plot
model8trim=trimfill(model8,data=HIVdata)
funnel(model8trim)
#Regimen NRTI on outcome variable TG:
model9<-
rma(d.ex.,var_d.ex.,subset=(trt==1&Outcome==9),data=HIVdata,method="REML")
model9
#pub bias for NRTI and TG:
#Egger's
regtest(model9,model="lm",data=HIVdata)
#Begg's
ranktest(model9,data=HIVdata)
#funnel plot
```

```
model9trim=trimfill(model9,data=HIVdata)

funnel(model9trim)
```

Multilevel MA R code for outcome HDL

```
library ("metafor")

#Calculate total number of participants (Ni)
HIVhdl$Ni <- unlist(lapply(split(HIVhdl,HIVhdl$study),function(x) rep(sum(x$n1i)+
x$n2i[1],each=nrow(x))))

##Creating the Variance-Covariance Matrix for Multiple Comparisons
calc.hdlv <- function(x) {
  hdlv <- matrix(1/x$n2i[1] + outer(x$d.ex., x$d.ex.,
"*")/(2*x$Ni[1]),nrow=nrow(x),ncol=nrow(x))
  diag(hdlv) <- x$var_d.ex.
  hdlv
}
hdlV <- lapply(split(HIVhdl,HIVhdl$study), calc.hdlv)
hdlV <- as.matrix(bdiag(hdlV))
hdlV

##Calculating the Weighted Mean ES for HDL Change (Multiple treatments),
Following Random-Effects Assumptions
HIVhdl$trt <-as.factor(HIVhdl$trt) (note: code for conversion from integer to
factor)
dhdl <- rma.mv(d.ex.,var_d.ex.,hdlV,mods = ~ factor(trt) - 1,random = ~ trt | study,
struct="UN", data=HIVhdl,method="ML")
dhdl
```

Multilevel Moderation analysis:

```
##Special note: We have to run multilevel code for variance co-variance matrix, the
n moderation code each time for all outcome variables.

R code considering week as a moderator for HDL:
hdl<-rma(d.ex.,var_d.ex.,hdlV,mods = ~ factor(trt) - 1 + HIVhdl$Weeks,data = HIVhdl
,method="ML")
hdl


R code for LDL:
ldl<-rma(d.ex.,var_d.ex.,ldlV,mods = ~ factor(trt) - 1 + HIVldl$Weeks,data = HIVldl,m
ethod="ML")
```

ldl

R code for TG:

```
tg<-rma(d.ex.,var_d.ex.,tgV,mods = ~ factor(trt) - 1 + HIVtg$Weeks,data = HIVtg,met
hod="ML")
tg
```

R code for Cholesterol:

```
chol<-rma(d.ex.,var_d.ex.,cholV,mods = ~ factor(trt) - 1 + HIVchol$Weeks,data = HIV
chol,method="ML")
chol
```

R code for Trunk:

```
trunk<-rma(d.ex.,var_d.ex.,trunkV,mods = ~ factor(trt) - 1 + HIVtrunk$Weeks,data =
HIVtrunk,method="ML")
trunk
```

R code for Limb:

```
limb<-rma(d.ex.,var_d.ex.,limbV,mods = ~ factor(trt) - 1 + HIVlimb$Weeks,data = HI
Vlimb,method="ML")
limb
```

Methodological quality as a moderator

R code considering week as a moderator for HDL:

```
hdl<-rma(d.ex.,var_d.ex.,hdlV,mods = ~ factor(trt) - 1 + HIVhdl$mq,data = HIVhdl,m
ethod="ML")
 hdl
```

R code for LDL:

```
ldl<-rma(d.ex.,var_d.ex.,ldlV,mods = ~ factor(trt) - 1 + HIVldl$mq,data = HIVldl,meth
od"ML")
ldl
```

R code for TG:

```
tg<-rma(d.ex.,var_d.ex.,tgV,mods = ~ factor(trt) - 1 + HIVtg$mq,data = HIVtg,method
="ML")
tg
```

R code for Cholesterol:

```
chol<-rma(d.ex.,var_d.ex.,cholV,mods = ~ factor(trt) - 1 + HIVchol$mq,data = HIVcho
l,method="ML")
```

```
chol
```

R code for Trunk:

```
trunk<-rma(d.ex.,var_d.ex.,trunkV,mods = ~ factor(trt) - 1 + HIVtrunk$mq,data = HI
Vtrunk,method="ML")
trunk
```

R code for Limb:

```
limb<-rma(d.ex.,var_d.ex.,limbV,mods = ~ factor(trt) - 1 + HIVlimb$mq,data = HIVli
mb,method="ML")
limb
```

Publication year as a moderator

R code considering week as a moderator for HDL:

```
hdl<-rma(d.ex.,var_d.ex.,hdlV,mods = ~ factor(trt) - 1 + HIVhdl$Pub_Year,data = HIV
hdl,method="ML")
hdl
```

R code for LDL:

```
ldl<-rma(d.ex.,var_d.ex.,ldlV,mods = ~ factor(trt) - 1 + HIVldl$Pub_Year,data = HIVld
l,method="ML")
ldl
```

R code for TG:

```
tg<-rma(d.ex.,var_d.ex.,tgV,mods = ~ factor(trt) - 1 + HIVtg$Pub_Year,data = HIVtg,m
ethod="ML")
tg
```

R code for Cholesterol:

```
chol<-rma(d.ex.,var_d.ex.,cholV,mods = ~ factor(trt) - 1 + HIVchol$Pub_Year,data =
HIVchol,method="ML")
chol
```

R code for Trunk:

```
trunk<-rma(d.ex.,var_d.ex.,trunkV,mods = ~ factor(trt) - 1 + HIVtrunk$Pub_Year,dat
a = HIVtrunk,method="ML")
trunk
```

R code for Limb:

```
limb<-rma(d.ex.,var_d.ex.,limbV,mods = ~ factor(trt) - 1 + HIVlimb$Pub_Year,data =
HIVlimb,method="ML")
limb
```

Female as a moderator

R code for HDL:

```
hdl<-rma(d.ex.,var_d.ex.,hdlV,mods = ~ factor(trt) - 1 + HIVhdl$female,data = HIVhd
l,method="ML")
hdl
```

R code for LDL:

```
ldl<-rma(d.ex.,var_d.ex.,ldlV,mods = ~ factor(trt) - 1 + HIVldl$female,data = HIVldl,m
ethod="ML")
ldl
```

R code for TG:

```
tg<-rma(d.ex.,var_d.ex.,tgV,mods = ~ factor(trt) - 1 + HIVtg$female,data = HIVtg,met
hod="ML")
tg
```

R code for Cholesterol:

```
chol<-rma(d.ex.,var_d.ex.,cholV,mods = ~ factor(trt) - 1 + HIVchol$female,data = HIV
chol,method="ML")
chol
```

R code for Trunk:

```
trunk<-rma(d.ex.,var_d.ex.,trunkV,mods = ~ factor(trt) - 1 + HIVtrunk$female,data =
HIVtrunk,method="ML")
trunk
```

R code for Limb:

```
limb<-rma(d.ex.,var_d.ex.,limbV,mods = ~ factor(trt) - 1 + HIVlimb$female,data = HI
Vlimb,method="ML")
limb
```

Average mean age as a moderator:

R code for HDL:

```
hdl<-rma(d.ex.,var_d.ex.,hdlV,mods = ~ factor(trt) - 1 + HIVhdl$avrg_mean_age,data
= HIVhdl,method="ML")
hdl
```

R code for LDL:

```
ldl<-rma(d.ex.,var_d.ex.,ldlV,mods = ~ factor(trt) - 1 + HIVldl$avrg_mean_age,data = HIVldl,method="ML")
ldl
```

R code for TG:

```
tg<-rma(d.ex.,var_d.ex.,tgV,mods = ~ factor(trt) - 1 + HIVtg$avrg_mean_age,data = HIVtg,method="ML")
tg
```

R code for Cholesterol:

```
chol<-rma(d.ex.,var_d.ex.,cholV,mods = ~ factor(trt) - 1 + HIVchol$avrg_mean_age,data = HIVchol,method="ML")
chol
```

R code for Trunk:

```
trunk<-rma(d.ex.,var_d.ex.,trunkV,mods = ~ factor(trt) - 1 + HIVtrunk$avrg_mean_age,data = HIVtrunk,method="ML")
trunk
```

R code for Limb:

```
limb<-rma(d.ex.,var_d.ex.,limbV,mods = ~ factor(trt) - 1 + HIVlimb$avrg_mean_age,data = HIVlimb,method="ML")
limb
```