Systematic Review And Meta-Analysis
Effect Of Vitamin D Supplementation With Anti-Viral Therapy On CD4 Levels In HIV-Infected Patients: Systematic Review And Meta-Analysis

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Abstract:

Introduction: Due to the effect of vitamin D on the immune response, There are controversial results about the effect of vitamin D supplementation on the immune system of AIDS patients. This systematic review and meta-analytical was conducted to determine the effect of vitamin D supplementation, along with antiretroviral treatment on CD4 count of HIV-infected patients.

Methods: This systematic review and meta-analysis study was done with using specific keywords HIV and vitamin D and CD4 and related keywords on published articles by the end of 2017 in the some databases such as Pubmed (116 articles), Scopus (121 articles) and Web of Science (127 articles). All articles have been export to ENDNOTE and after deleting duplicate, there was 174 articles. Review selected articles by two individuals, first on the title and abstract. Clinical trial studies about vitamin D supplementation on HIV-infected patients which receiving ART were selected. Quality assessment of studies was conducted by Jadad criteria. CD4 count and viral load before and after intervention in treatment and placebo groups, age of patients and duration of intervention were extracted.

Fiundings: Finally, 7 clinical trial studies with a sample size of 639 people were entered the meta-analysis. The mean age of patients in the treatment group and placebo was 27.2 and 26.5 years respectively, and mean duration of intervention was 8.3 months. The increase in CD4 after treatment was 0.73 (CI95%:-0.43 - 1.89) compared with the placebo group which was not statistically significant, but Vitamin D use in 3 studies was near one year and this change (SMD=3.56, CI95%: 1.17-5.96) was significantly in these studies. Egger's test results showed that there was no publication bias.

Conclusion: The results showed that at least 10 months use of vitamin D supplementation with antiviral therapy can effectively help in increasing the CD4 level in comparison with placebo.

Keywords: Vitamin D, Antiviral treatment, CD4, AIDS, HIV

Introduction:

In 2015, HIV/AIDS was the 12th most common cause of death worldwide, and according to estimates, 1.2 million people died of HIV/AIDS in this year (1). According to the global epidemiological study of AIDS in 2014, the overall incidence rate of this disease in people aged 15 to 49 years was reported to be 0.05%, and the highest incidence of HIV/AIDS was reported in sub-Saharan Africa and then, in Asia (2). This disease causes opportunistic infections and cancers in affected people by weakening the immune system (3).

Vitamin D is a fat-soluble vitamin that plays a major role in proliferation, and

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differentiation of immune cells and regulation of immune responses (4, 5). Laboratory studies indicate the crucial role of this vitamin in regulating the immune system and increasing T cell count. The function of vitamin D as an immunoregulator has been suggested (6). Vitamin D affects the immune system by affecting endogenous antibiotics called antimicrobial peptides (AMP) and through proliferation of T cells (7). In HIV, the HIV virus leads to the destruction of T cells, and vitamin D increases the intrinsic immunity of the body by contributing to the production of immune cells and contributing to their function (8). The causes of vitamin D deficiency in non-infected individuals also apply to HIV patients. In addition, HIV patients suffer from defective renal hydroxylation, and cannot convert 25-hydroxyvitamin D to its active form. It has been observed that taking antiretroviral drugs increases metabolism and decreases vitamin D levels (9). In a cohort study by Christine in the United States (2003 to 2006), it was reported that vitamin D levels in HIV patients were lower than healthy subjects and vitamin D levels in patients undergoing antiretroviral treatment and patients who did not receive this treatment were lower than normal level. In addition, vitamin D levels were lower in patients who took antiretroviral drugs compared to those who did not receive treatment (10). In a study by Lattuuada et al. in Italy in 2009, the result of the study demonstrated the ineffectiveness of antiretroviral drugs on vitamin D levels (11). Furthermore, Brown and McComsey (2010) conducted a study in the United States to investigate the relationship between vitamin D levels and antiretroviral drugs; vitamin D levels were measured in HIV patients before the beginning of antiretroviral therapy, and 6 to 12 months after that. The results indicated a significant reduction in vitamin D levels after the use of antiretroviral drugs (12).

Considering low vitamin D levels in patients with HIV, contradictory results have been reported in studies on the effect of vitamin D on the immune system of patients with AIDS. Therefore, the present systematic review and meta-analysis was conducted to evaluate the effect of vitamin D supplements and antiviral treatment on CD4 counts in HIV patients.

Methods:

This study is a systematic review and meta-analysis that was performed in clinical trial about the effect of vitamin D copmpared with placebo on CD4 count of HIV-infected patients that was recieved antirevial therapy. Systematic search was conducted in the databases, include: Pubmed, Scopus, web of sciences until end of 2017. In Pubmed and scopus, we used keywords in Title/Abstract field. In web of sciences, we used keywords in topic field. Our query include (HIV OR "Human Immunodeficiency Virus" OR AIDS OR "Acquired Immune Deficiency Syndrome Virus") AND CD4 AND "Vitamin D" and keywords extracted from MESH. All document search was exported to Endnote and then duplicate document was deleted. In screenig, for study selection, two independent, blinded investigators reviewed the title and abstracts of all study, respectively. Disagreements between

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reviewers were resolved by discussion. Study quality was assessed using Jadad score and score 3-5 were considered good quality and less than 3 as poor quality. For data extraction, data were extracted by two independent and Blinded authors and recorded in checklist. Disagreements between authors were resolved by discussion. Data extraction form contains author, publication year, sample size in intervention and placebo group, CD4 count befor and after treatment, viral load, patients age, vitamin D dosage and route of administration. Data were analyzed by STATA 11.1 and we used random effect method. Heterogeneity was checked by I2 index. Publication biases was evaluated by Egger tests.

Findings:

Finally, we enrolled 7 studies in this meta-analysis and PRISMA flowchart for inclusion of studies in the meta-analysis shown in figure 1. Characteristics of these studies are shown in Table 1. Generally, 639 patients include 355 patients in the intervention group and 304 patients in placebo group were studied. The mean age of patients in the intervention and placebo groups was 27.2 and 26.5 years, respectively, and the mean follow up time was 8.3 months. Four of 7 studies have good quality by Jadad score. As shown in Figure 2, the increase in CD4 count after treatment with vitamin D compared to placebo was 0.73 (CI95%: -0.41 - 1.89), which wasn't statistically significant and the hetrogenity I2 index was 97.4%. Egger test shows that there wasn't publication bias for CD4 result in published study (P=0.366). Figure 3 shows that the decrease in viral load after vitamin D treatment compared to placebo was -0.17 (CI95%: -2.53 - 2.19), which wasn't statistically significant and hetrogenity I2 index was 97.7%. Egger test show that there wasn't publication bias for viral load result in published study (P=0.938).

Vitamin D use in 3 studies was near one year and figure 4 show that CD4 count difference (SMD=3.56, CI95%: 1.17-5.96) after treatment in these studies increased significantly in vitamin D group compared to placebo.

Discussion:

This systematic review and meta-analysis showed that the increase in CD4 count after treatment with vitamin D wasn't statistically significant compared to placebo, but, Vitamin D supplementation use for about one year, have consistent benefits on either mean CD4+ cell count. Similar to our result, Forrester et al, in a narrative review about micronutrient intake in HIV-positive adults focused primarily on the results of nine trials of multiple micronutrient supplementation; seven trials in non-pregnant HIV-positive adults, and two in pregnant HIV-positive women. The authors reported that "five of the six trials that used high-dose multiple micronutrients showed benefits in terms of either improved CD4 cell counts or survival", but also that "many of these trials were small and of short duration, and the long-term risks and benefits of high-dose multiple micronutrients are not established" (20). In another narrative review by Jiménez-Sousa et al, suggests that Vitamin D supplementation seems to reverse some alterations of the immune system,

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supporting the use of Vitamin D supplementation as prophylaxis, especially in individuals with more severe Vitamin D deficiency (21). However, Visser et al, in one Cochrane Review show that the analyses of the available trials have not revealed consistent clinically important benefits with routine multiple micronutrient supplementation in people living with HIV. Larger trials might reveal small but important effects. These findings should not be interpreted as a reason to deny micronutrient supplements for people living with HIV (22). Regarding the lack of effect of vitamin D supplementation in some studies, it can have several causes, including: The period of intervention may have been insufficient to demonstrate effects, with benefits only accruing over prolonged periods of supplementation. intervention ranged from 3 months up to one year and subgroup analysis confirmed this hypothesis and as an another possible cause, the doses supplemented varied considerably and in this systematic review, highest impact was observed in the Stallings study, which used the highest dose of vitamin D among trials.

The present study shows that there wasn't statistically significant in the decrease of viral load after vitamin D treatment compared to placebo. In similar to the present study, Visser et al, reported that routine supplementation for up to two years may have little or no effect on the average of mean viral load (22).

Finally, the results of this study indicate that at least 10 months use of vitamin D supplementation with antiviral therapy can effectively help in increasing the CD4 level in comparison with placebo and it is recommended that a dose-response meta-analysis study be conducted to evaluate the efficacy of different doses of vitamin D or multi-center clinical trial study be designed about the efficacy of high dose of vitamin D.

Acknowledgments: The authors would like to thank of Reza Alizadeh-Navaei for statistical analysis

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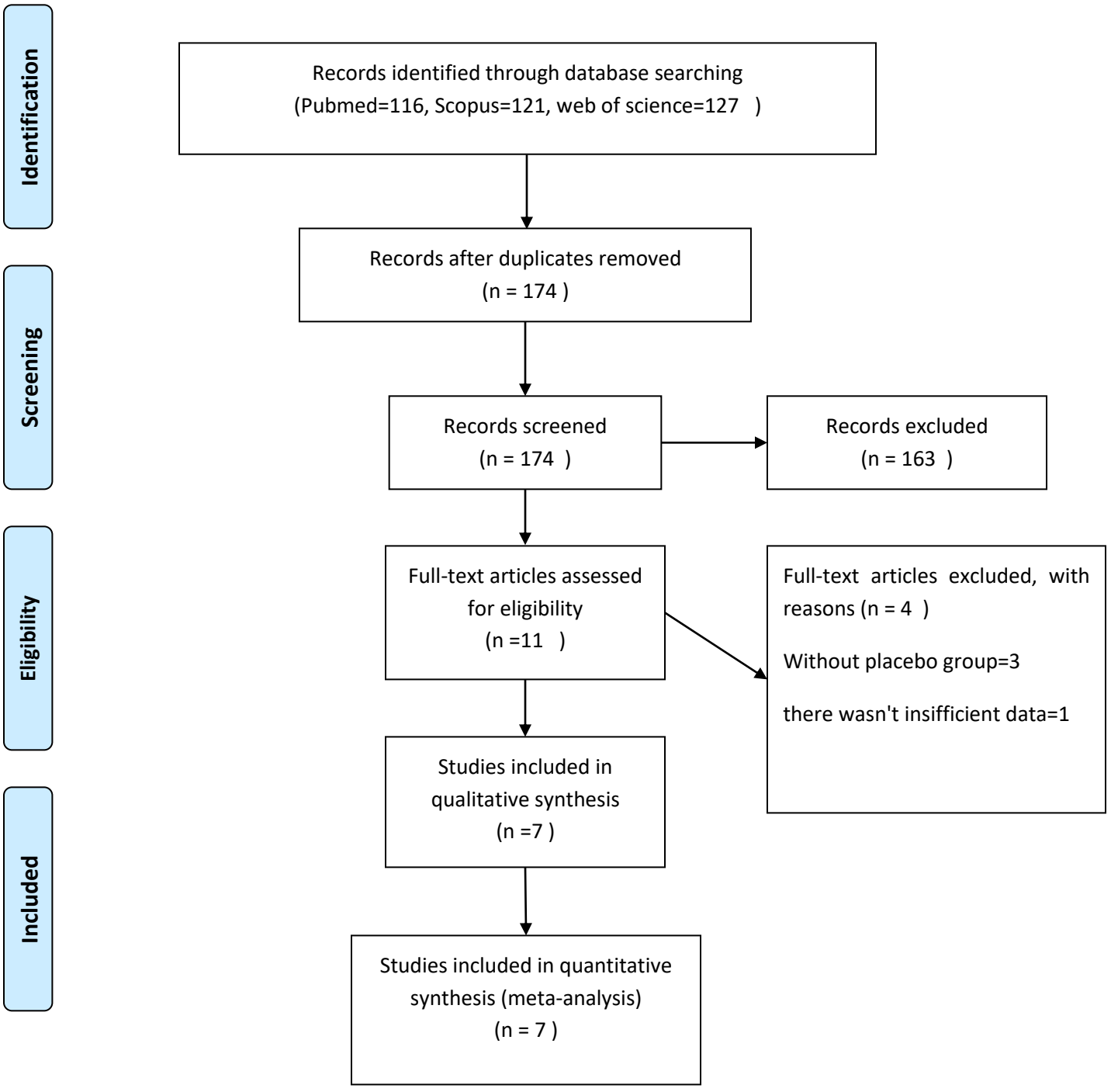
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Figure 1: PRISMA flowchart for inclusion of studies in the meta-analysis



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Table 1: Characteristics of inclusion of studies in the meta-analysis

Study	Year	N		CD4 Mean (SD)				Viral load Mean (SD)				Mean age		Follow up time	Intervention	Jadad score
				Intervention		Placebo		Intervention		Placebo						
		Intervention	Placebo	Before	After	Before	After	Before	After	Before	After	Intervention	Placebo			
Steenhoff (13)	2015	30	30	758 (540)	693 (451)	820 (421)	765 (334)	1.7 (0.62)	1.55 (0.54)	1.46 (0.2)	1.57 (0.62)	19.5	19.5	3	4000-7000 daily	5
Stallings (14)	2015	28	27	616 (190)	646 (222)	784 (288)	612 (20)	3.29 (0.92)	3.12 (0.81)	3.06 (1.02)	3.78 (1.06)	21.3	20	12	7000 daily	2
Overton (15)	2015	79	86	346 (42.8)	551 (53.1)	337 (33.6)	526 (53.6)	4.5 (0.16)		4.5 (0.18)		36	31	12	4000 daily	3
Falasca (16)	2014	67	39	595.9 (283.3)	626 (303.2)	541.5 (298.6)	581.5 (312.3)	-	-	-	-	45.2	45.7	10	300000 mothly oral	2
		47		585.4 (271.5)	586.8 (231.6)			-	-	-	-	44.2	45.7	10	25000 mothly IM	2
Kakalia (17)	2011	18	17	799 (411)	774 (413)	862 (392)	882 (503)	1.22 (0.27)	1.8 (0.25)	1.63 (0.29)	1.68 (0.26)	10.6	10.7	6	800 daily	2
		18		1115 (545)	945 (351)			0.8 (0.27)	0.8 (1.55)	1.63 (0.29)	1.68 (0.26)	10.3	10.7	6	1600 daily	2
Bang (18)	2012	19	22	507 (268)	511 (538.1)	463 (197)	483 (213)	-	-	-	-	48	45	4	100000	4
Arpadi (19)	2009	29		771 (328)	776 (359)	719 (382)	661 (363)	2.8 (0.9)	2.4 (0.9)	2.9 (1)	2.5 (1.1)	10.2	10.6	12	100000 biomonthly	3

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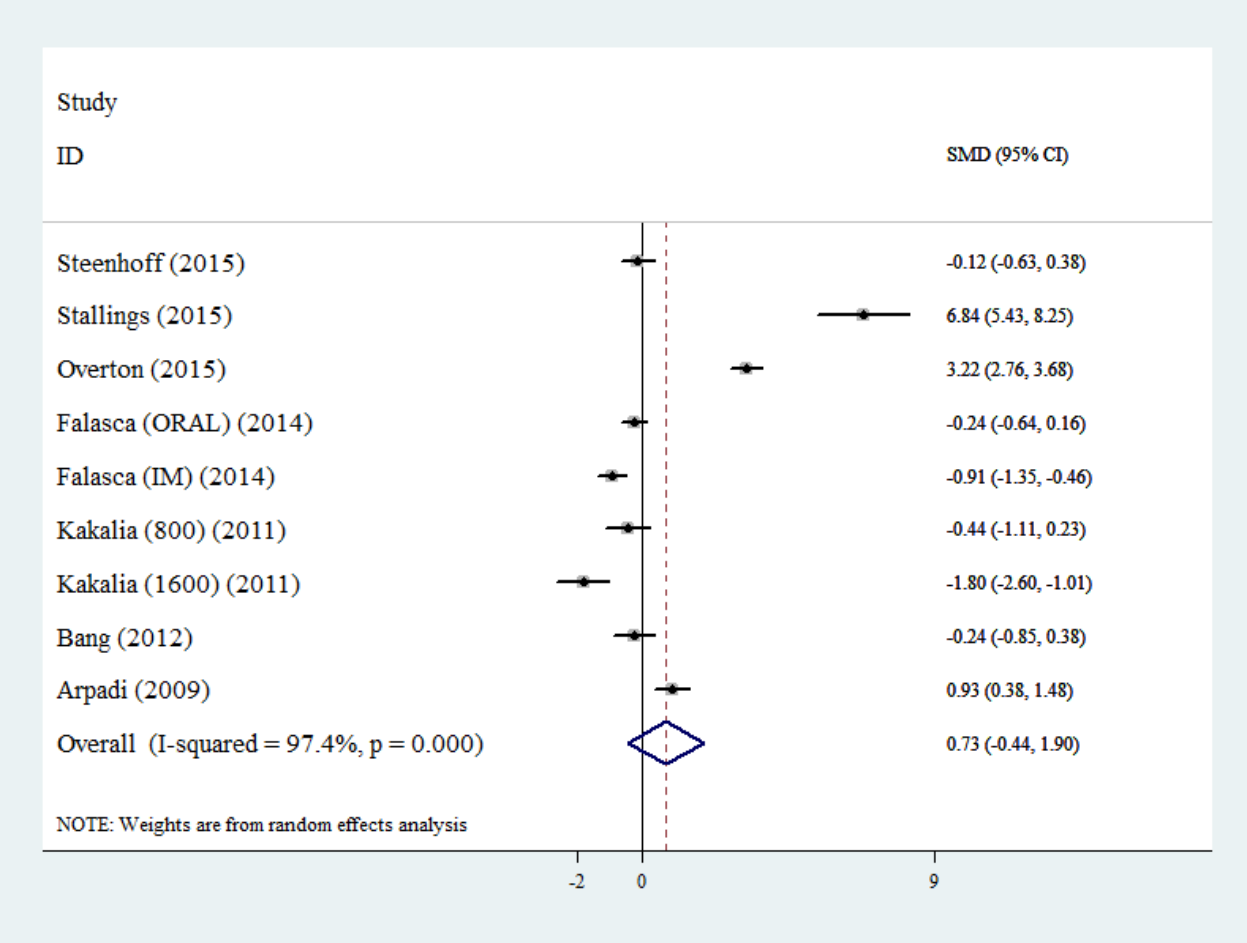


Figure 2: Forest plot for CD4 count difference after treatment with vitamin D compared to placebo

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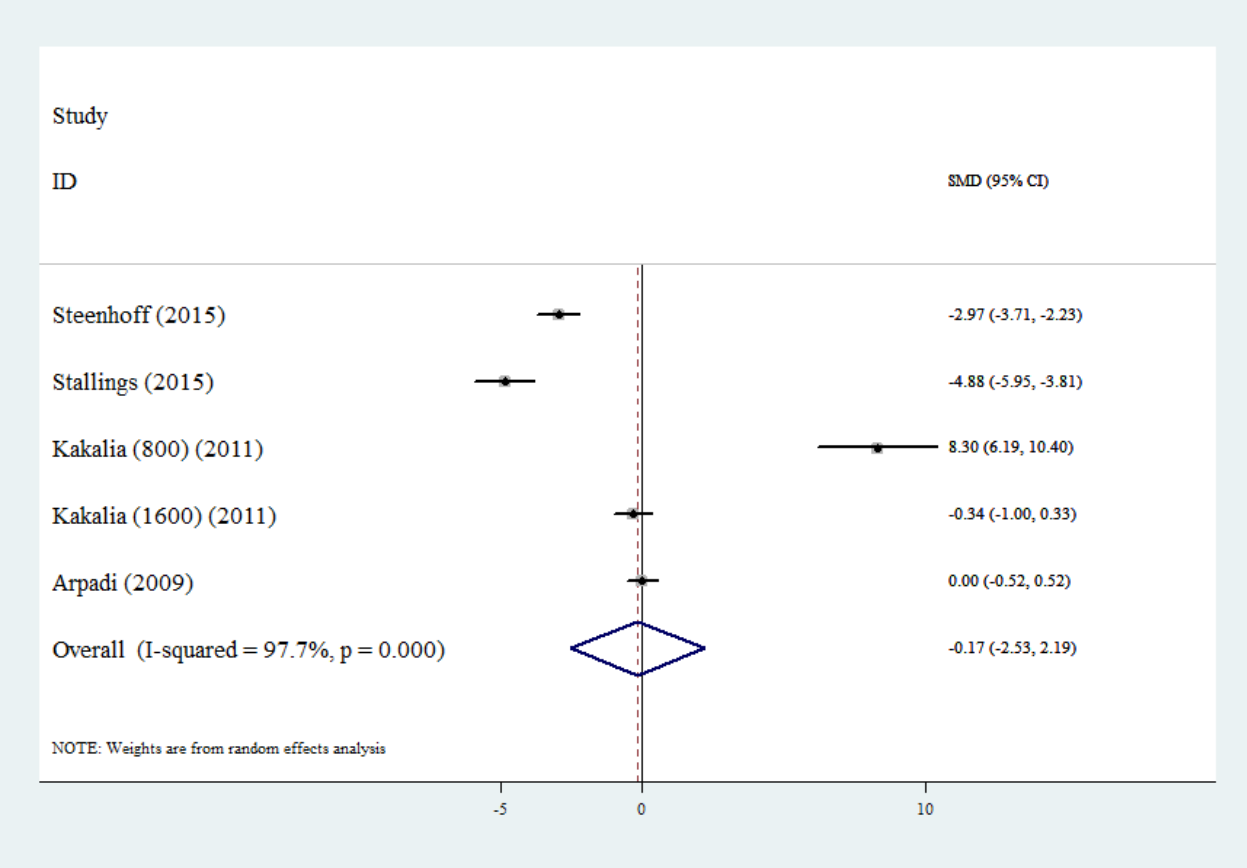


Figure 3: Forest plot for viral load difference after treatment with vitamin D compared to placebo

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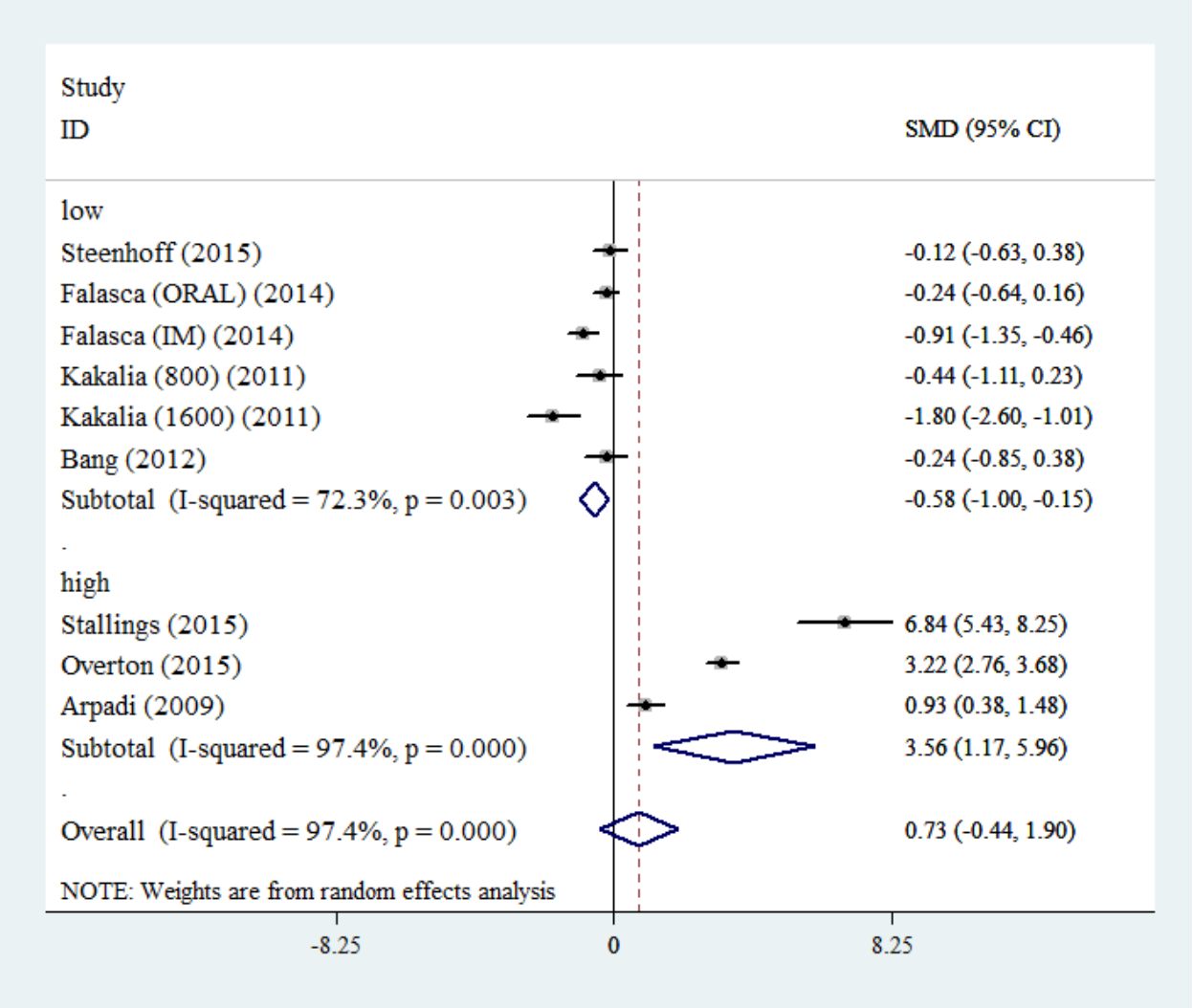


Figure 4: Forest plot for CD4 count difference after treatment with vitamin D compared to placebo by duration of vitamin D use

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