International Journal of Research
Available at https://edupediapublications.org/journals
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 04 Issue 09
August 2017

Effect of low dose corticosteroids in HIV disease progression: systematic review

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Abstract

Background: *Despite the success of antiretroviral therapy on reduction of mortality in HIV infection, HIV-infected patients treated with HAART still have a life expectancy below the average of the uninfected population. Immune activation plays an important role in the pathogenesis of HIV infection. An increasing body of data has clearly demonstrated that, despite 'undetectable' viral load levels following initiation of therapy, there remains evidence of persistent immune activation.* ***Objectives:*** *To establish whether low dose corticosteroids could decrease HIV disease progression.* ***Methods:*** *Electronic searches were undertaken through CENTRAL, CINHAL, Scopus, PubMed, LILACS and Web of Social Science. In addition, we used abstracts from numerous relevant conferences, including the International AIDS Conferences and the annual Conferences on Retroviruses and Opportunistic Infections were searched. We combined data for outcomes from studies that meet the inclusion criteria in the meta-analysis using the latest version of Review Manager Software, provided the studies are sufficiently similar. As all outcomes were continuous data, we used random effects meta-analysis to produce the overall results. JLT and JLT independently assessed the risk of bias for each trial using a simple form and followed the domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Intervention.* ***Main results:*** *Thirty eight of 2145 articles were selected and evaluated for their titles and abstracts in relation to the inclusion and exclusion criteria. After duplicate references were eliminated, 9 articles remained and 5 articles were included in meta-analysis. The calculated mean difference of CD4 count (10^6 cells/ml) between low dose corticosteroids group and control was -117.99 [-230.27, -5.72; p-value= 0.04). The viral load mean difference (10^4 RNAc/ml) between low dose corticosteroids group and control was 0.77 [-0.01, 1.55; p-value=0.05]. Low dose corticosteroids seems to decrease HIV disease progression with the mean difference of plasma TNF-alpha(pg/ml) at 4 weeks between low dose corticosteroids group and control was -12.65 [-19.75, -5.55; p=0.0005] and -9.72 [-16.61, -2.83; p=0.006] at 8 weeks between . Therefore, low dose corticosteroids did not show any effect on Il-6 within 4 and 8 weeks of intervention.* ***Conclusions:*** *In conclusion, the administration of low dose CSs in HIV-infected patients could not be judged as ameliorating HIV disease progression. In fact, this review included many limitations. However, more RCTs are needed to establish clinical consensus.*

Key words: corticosteroids; HIV disease progression; antiretroviral therapy

Background

2.1 million [1.8 million–2.4 million] newly HIV infected people were noticed worldwide, increasing then a total of 36.7 million [34.0 million–39.8 million] people already living with HIV in 2016 and 1 million [830 000–1.2 million] people died from HIV-related illnesses in 2016 (WHO 2016). In addition, the number of people living with HIV on antiretroviral therapy has increased by about a third, reaching then 17.0 million people (WHO 2016). However, the dramatic success of antiretroviral therapy on reduction of mortality in HIV infection, HIV-infected patients treated with HAART still have a life expectancy below the average of the uninfected population (Lohse 2008; Kasang 2012). Immune activation plays an important role in the pathogenesis of HIV infection. An increasing body of data has clearly demonstrated that,

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despite 'undetectable' HIV-RNA plasma levels following initiation of therapy, there remains evidence of persistent immune activation is obvious (Green 2015). HIV-1 infection is characterized by T cell activation, inflammation and hyper-coagulation. Yet, effects of antiretroviral therapy (ART) on dynamics of these indices and correlates of CD4 cell reconstitution are incompletely understood (Funderburg 2013). Studies have illustrated that bio-markers of inflammation and coagulation are potential candidates for improving risk prediction of HIV disease progression (Neaton 2010; Worm 2010). These markers, including C-reactive protein, interleukin-6, and D-dimer are reported to be higher in untreated as well as treated HIV-infected individuals compared to HIV-negative individuals (Baker 2010; Neuhaus 2010). Those bio-markers are associated with the risk of all-cause mortality, independently of CD4 cell count and viral load levels (Neaton 2010; Kuller 2008; Tien 2010; Achhra 2013). Based on this evidence, immune-based therapies that focus on reducing immune activation under HAART may therefore further close this gap (Kasang 2012). This study has shown that factors of general immune activation associated with HIV disease progression and found significantly lower bio-markers levels in patients receiving prednisolone compared to untreated patients, suggesting that prednisolone may have beneficial effects on immunological correlates of HIV disease progression (Kasang 2012). Three uncontrolled studies conducted in this field before highly active antiretroviral therapies have illustrated a potentially beneficial effect of corticosteroids (CSs) on HIV disease in the absence of opportunistic infection. In a study reported by Ferdman and Church in 1994 (Ferdman 1994), five HIV-infected children with CD4 cell counts below 500 cells/ml and p24 antigenemia at baseline were treated with prednisone. The results have shown that serum p24 antigen levels lower significantly during the treatment.

The above mechanisms could be explained clearly by figure 1: the levels of plasma markers related to inflammation and coagulation. Chronic HIV disease produces a procoagulant state may include mechanisms related to activation of the innate and adaptive immune system by low level HIV replication, co-pathogens, and microbial products translocated from the gastrointestinal tract. As described above, inflammatory bio-markers are the main cause of HIV disease progression.

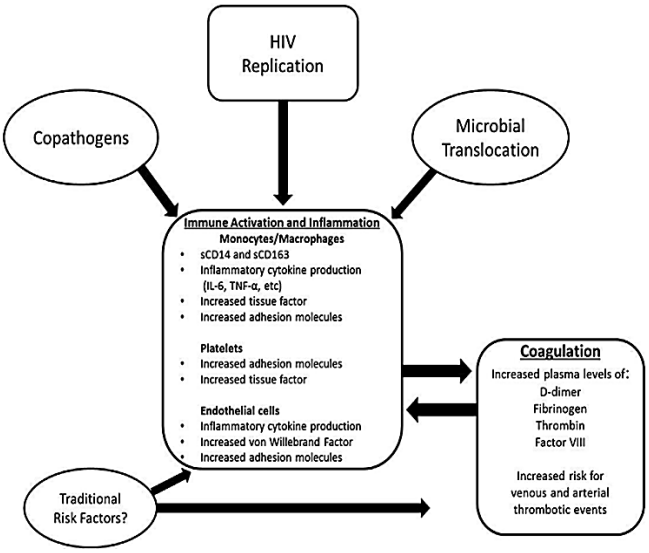

Fig 1. The relationships between coagulation and inflammation in HIV disease progression.

On the basis of the results of previous clinical trials, a systematic review was conducted by (Briel 2006), which demonstrated the feasibility of adjunctive corticosteroid treatment for the treatment pneumocystis pneumonia (PCP) in patients co-infected with HIV. Therefore, adjunctive CSs therapy has been recommended by the American CDC Guidelines to treat PCP associated with HIV-1 infection (Kaplan 2009). However, corticosteroid therapy may increase the occurrence of opportunistic infections, by causing deterioration of cell-mediated immunity (Wolfe 2006; Ko 2015). Systemic CSs are frequently used in individuals with severe lymphopenia and active opportunistic infections (OIs) as adjunctive therapy for OI management among which pneumocystis pneumonia (PCP), cerebral toxoplasmosis, and tuberculous meningitis or for treatment of Immune Reconstitution Inflammatory Syndrome (IRIS) (Grant 2015). Recently, few studies have been conducted to investigate the use of CSs in HIV disease progression. Therefore, the results have been inconclusive. The present meta-analysis aimed to evaluate the effects of low dose CSs treatment on HIV disease progression.

Objectives

The aim of this systematic review was to evaluate the effect of corticosteroids (CSs) administration on HIV disease progression.

Methods

Criteria for considering studies for this review

Types of studies

We included randomized control trials, prospective cohort studies, quasi-randomized control trials and non-randomized control trials that evaluate the use of CSs in HIV disease progression.

Types of participants

This review included HIV-infected adults' patients.

Types of interventions

The interventions were based on low dose of corticosteroids administration: prednisone and prednisolone were included in different studies.

Types of outcome measures

Primary outcomes

- CD4 count
- Viral load

Secondary outcomes

Inflammatory mediators:

- TNF-alpha
- Il-6

Search methods for identification of studies

Electronic searches

Electronic searches were undertaken using the following databases CENTRAL, CINHAL, Scopus and PubMed, LILACS, and Web of Social Science. Hand searches of the reference lists of all pertinent reviews and studies found were also undertaken. Abstracts from numerous relevant conferences, including the International AIDS Conferences and the annual Conferences on Retroviruses and Opportunistic Infections were searched.

Furthermore, we searched trials registries through the World Health Organization International Clinical Trials Platform Search Portal (http://apps.who.int/trialsearch/Default.aspx).
We will also search the following electronic data base:
• AIDSInfo® (http://www.aidsinfo.nih.gov/).
• The International AIDS Society Conference on HIV Pathogenesis and Treatment
• International AIDS Conference (available at http://www.iasociety.org).
• Conference on Retroviruses and Opportunistic Infections (CROI),
• Interscience Conference on Antimicrobial Agents & Chemotherapy (ICAAC),
• The European AIDS Clinical Society (EACS)

The entire above search was done without any language restrictions.

Data collection and analysis

Selection of studies

Two authors (JLT and JLT) independently identified citations and abstract of references to establish whether the articles met inclusion criteria. Disagreement was resolved by discussion or by consulting JLT. In case that study potentially met the inclusion criteria based on the title, abstract or both, then full article was assessed.

Data extraction and management

JLT and JLT independently extracted data from the selected trials using standardized data extraction forms. The following data will be extracted:

• Study details: citation, start and end dates, location and study design.
• Participant details: study population eligibility (inclusion and exclusion) criteria, ages, population size, details of HIV diagnosis and disease and any clinical, immunologic or virologic staging or lab information.
• Interventions details: drug names, doses and duration. Outcome details: CD4 count, viral load, TNF-alpha and Interleukins.

In case of any disagreement, we resolved the disagreement by discussion.

Assessment of risk of bias in included studies

JLT and JLT independently assessed the risk of bias for each trial using a simple form and will follow the domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Intervention (Higgins 2011). We will compare the assessment results and discuss any discrepancies between ourselves. We aim to achieve agreement on the final assessment for each decision by discussion.

The following domains will be assessed as low risk of bias, unclear risk of bias or high risk of bias: Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessor, Incomplete outcome data, Selective reporting and Other bias

We used the following definitions:

Generation of allocation sequence

- low risk of bias, if the allocation sequence was generated by random number table, computer random number generator, coin tossing, throwing dice, drawing of lots, shuffling cards or envelopes or minimization.
- unclear risk of bias, if there is insufficient information about the sequence generation process
- High risk of bias, if a system involving dates, names, or admittance numbers was used for the allocation of patients.

Allocation concealment

- Low risk of bias, if the allocation of patient involved a central independent unit, on-site locked computer, sequentially numbered drug containers of identical appearance prepared by an independent pharmacist or investigator, or opaque sealed envelopes.
- Unclear risk of bias, if the trial was described as randomized, but the method used to conceal the allocation was not described.
- High risk of bias, if there is insufficient information about the allocation concealment process to permit judgment.

Blinding

- Low risk of bias, if there is no blinding but the outcome and the outcome measurement are not likely to be influenced by lack of blinding, if blinding of participants and key study personnel ensured and unlikely that the blinding could have been broken, if either participants or some key personnel were not blinded but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
- Unclear risk of bias, if there are insufficient information to permit judgement or if the study did not address this outcome.
- High risk of bias, if no blinding or incomplete blinding was done and the outcome or outcome measurement is likely to be influenced by lack of blinding, if blinding of key study participants and personnel was done but likely that the blinding could have been broken, if the participants or some key study personnel were not blinded which could have introduced bias.

Incomplete outcome data

- Low risk of bias, if there are no missing outcome data, reason for missing outcome data unlikely to be related to true outcome, missing outcome data balanced in numbers across intervention groups.
- Unclear risk of bias, if there is insufficient reporting of attrition/exclusions to permit judgement of the study did not address this outcome.
- High risk of bias, if reason for missing outcome data likely to be related to true outcome, imbalance in the numbers or reason for missing data across intervention groups.

Selective outcome reporting

- Low risk of bias, if the study protocol is available and all the pre-specified outcomes of interest have been reported

of if study protocol is not available but published reports include all expected outcomes.
- Unclear risk of bias, if there is insufficient information to permit judgement.
- High risk of bias, if not all the pre-specified primary outcomes have been reported.

Other potential threats to validity

- Low risk of bias, if the study appears to be free of other sources of bias.
- Unclear risk of bias, there may be a risk of bias but there is insufficient information to prove it.
- High risk of bias, if there is at least one important risk of bias.

Measures of treatment effect

Statistical analysis was performed according to the statistical guidelines referenced in the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2011). As only continuous outcomes were included, the measure of effect was expressed as a mean difference (MD) with 95% CI.

Unit of analysis issues

The unit of analysis was individuals. A single measurement for each outcome from each participant was collected and analyzed.

Assessment of heterogeneity

We first assessed clinical and methodological heterogeneity as described in the Cochrane Handbook for Systematic Reviews of Intervention. We used the I^2 statistic to measure statistical heterogeneity among the trials in each analysis. And then, we identified substantial heterogeneity we explored it by pre-specified subgroup analysis. The I^2 statistic describes the percentage of total variation across trials that are due to heterogeneity rather than sampling error (Higgins 2003). We considered there to be significant statistical heterogeneity in case that I^2>50% (Higgins 2011). As we included several studies design, different stage of HIV stages participants and different intervention, we expected heterogeneity to be high in the overall results.

Data synthesis

We combined data for outcomes from studies that met the inclusion criteria in the meta-analysis using the latest version of Review Manager Software, provided the studies were sufficiently similar in participants, interventions, outcomes and comparison. We used random effects to conduct meta-analysis. As we only included continuous outcomes, the measure of effect was expressed as a mean difference (MD) with 95% CI.

Results

Description of studies

After search strategy, 2145 articles were selected. Among them 38 studies were selected and evaluated for their titles and abstracts in relation to the inclusion (see table 1: Characteristics of included studies) and exclusion criteria (see table 2: Characteristics of excluded studies). After duplicate references were eliminated, 9 articles remained and 5 articles were included in meta-analysis.

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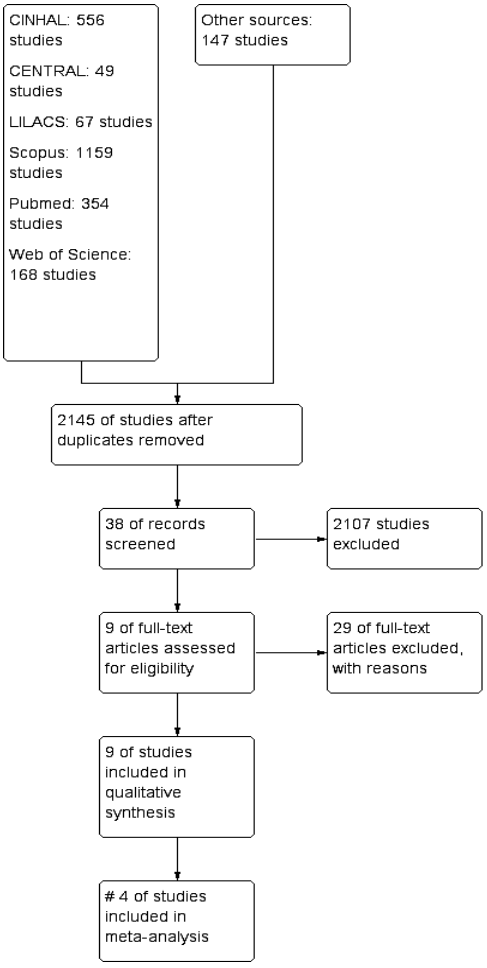

Figure 2: flow diagram

Table 1: Characteristics of included studies

Andrieu 1995				
Study designs	Participants	Interventions	Outcomes	Bias assessment
Trial with before and after intervention	HIV seropositive determined by ELISA and Western blot; aged 20-60 years; CDC class II or class III (lymphadenopathic. blood CD4 lymphocyte count of 200-199/microL.	Oral prednisolone (Solupred; Laboratoire Houde, Puteaux, France) was given at a daily dose of 0.5 mg/kg before breakfast	CD4 cell count (mean ± SD) Viral load(mean ± SD)	Selection bias was high risk of bias. Performance, detection and attrition biases were judged as low risk of bias, and reporting bias was unclear. Lastly, confounders were not controlled.
Kasang 2012				
Prospective cohort study	HIV-1-infected subjects who receive neither HAART nor prednisolone and with detectable viral load. a) untreated patients (n = 10), b) patients being treated with low-dose prednisolone (n = 27), c) with HAART (n = 30), d) HAART plus prednisolone (N =	"untreated"; (2) HIV-1 infected subjects treated with 5 mg/day prednisolone, referred to as "Prednisolone"; (3)HIV-1 infected subjects treated with antiretroviral therapy, referred to as "HAART"; (4) HIV-infected subjects treated with	CD4 count (mean ± SD) Viral load (mean ± SD)	Selection bias was judged as high risk of bias. Performance bias was unclear. Detection, reporting and attrition biases were judged as low risk of bias. Confounders were not controlled.

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	31) or e) treatment-naïve patients with undetectable viral load	antiretroviral therapy in combination with 5 mg/day prednisolone, referred to as "HAART+ Prednisolone"		
Kasang 2016				
Double-blind, placebo-controlled randomized clinical trial	326 HIV-patients in a resource-limited setting in Tanzania. Inclusion criteria were a CD4 count > 300 cells/µl, the absence of AIDS-defining symptoms and an ART-naïve therapy status. A total of 326 patients were randomized; 163 study participants received placebo and 163 study participants received prednisolone.	The effects of prednisolone per os in a daily dose of 5 mg on HIV disease progression during the early phase HIV infection	CD4 (mean ± SD) HIV viral load(mean ± SD)	All domains were judged as low risk of bias.
McComsey 2001				
randomized, double-blinded, placebo-controlled trial	HIV-1 infected aged 18 years or over, blood CD4 cell count above 200 X 10^6 cells/l on ARV regimen for a minimum of 8 weeks prior to study entry. 41 enrolled patients, 39 were male and two were female. Prednisone group: 21 patients Control group: 20 patients	Prednisone at a daily dose of 0.5 mg/kg or placebo.	CD4(mean ± SD) Viral load (mean ± SD) Plasma TNF-Ɣ(mean ± SD) S-plasma IL-6 levels(mean ± SD)	Selection bias was low risk of bias. Performance was unclear. Detection, attrition and reporting biases were judged as low risk of bias.

Table 2: Characteristics of excluded studies

Study ID	Reasons of exclusion
Andrieu 2005	Retrospective cohort study
Ansari 2007	Experimental study
Orlikowsky 2001	Experimental study assessing other types of outcomes
Ulmer 2005	Retrospective cohort study

Table 3: Table of findings

Patient or population: HIV-infected adults patients Intervention: Low dose CSs					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (G	Comments
	Assumed risk	Corresponding risk				
	Co	CD4 count				

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Volume 04 Issue 09
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	ntrol		RADE)
CD4 count (106 cells/ml)	The mean CD4 count (106 cells/ml) in the intervention groups was 117.99 lower (230.27 to 5.72 lower)	516 (4 studies)	⊕⊕⊖⊖ low [1,2]
Viral load (104 RNAc/ml)	The mean viral load (104 rnac/ml) in the intervention groups was 0.77 higher (0.01 lower to 1.55 higher)	516 (4 studies)	⊕⊕⊖⊖ low [3,4]
Plasma TNF-alpha (pg/ml) at 4 weeks Follow-up: mean 4 weeks	The mean plasma tnf-alpha (pg/ml) at 4 weeks in the intervention groups was 12.65 lower (19.75 to 5.55 lower)	41 (1 study)	⊕⊕⊕⊖ moderate [5]
Plasma TNF-alpha (pg/ml) at 8 weeks Follow-up: median 8 weeks	The mean plasma tnf-alpha (pg/ml) at 8 weeks in the intervention groups was 9.72 lower (16.61 to 2.83 lower)	41 (1 study)	⊕⊕⊕⊖ moderate [6]
Plasma Il-6 level (pg/ml) at 4 weeks Follow-up: mean 4 weeks	The mean plasma il-6 level (pg/ml) at 4 weeks in the intervention groups was 0.62 lower (2.88 lower to 1.64 higher)	41 (1 study)	⊕⊕⊖⊖ low [7,8]
Plasma Il-6 level (pg/ml) at 8 weeks Follow-up: mean 8 weeks	The mean plasma il-6 level (pg/ml) at 8 weeks in the intervention groups was 0.52 lower (2.67 lower to 1.63 higher)	41 (1 study)	⊕⊕⊖⊖ low [6]

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;

GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

[1] There was an observational study and one trial that were included.
[2] Heterogeneity was above 75%
[3] an observational study and a trial were included
[4] Heterogeneity was above 75%
[5] the sample size was small
[6] No explanation was provided
[7] the study was low
[8] the null value was included

Effects of interventions

CD4 count: The calculated mean difference of CD4 count between low dose corticosteroids group and control was -117.99 [-230.27, -5.72]. Then, the mean difference was reduced to -117.99 CD4 count compared to low corticosteroids group (p-value=0.04); see figure 2.

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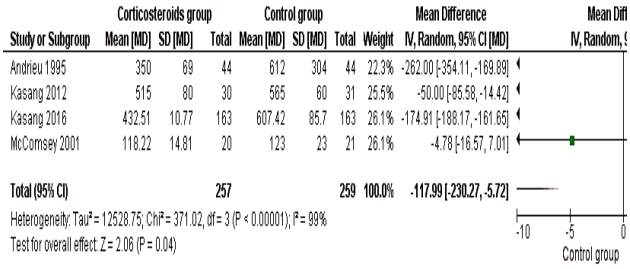

Figure 2: Forest plot of comparison: control group versus corticosteroids group; Outcome: CD4 count (10^6 cells/ml) [MD].

Viral load: The calculated mean difference of viral load between low dose corticosteroids group and control was 0.77 [-0.01, 1.55]. By the way, the mean difference was 0.77 RNAcc augmented in low corticosteroids group compared to the control group (p-value=0.05); see figure 3.

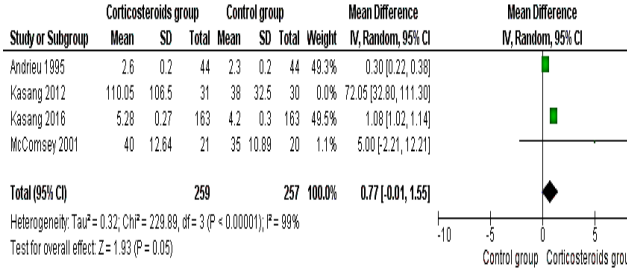

Figure 3: Forest plot of comparison: control group versus corticosteroids group; Outcome: Viral load (10^4 RNAc/ml).

TFN-alpha at 4 weeks: the calculated mean difference of plasma TNF-alpha at 4 weeks between low dose corticosteroids group and control was -12.65 [-19.75, -5.55] with p=0.0005. We can conclude that the mean difference of TNF-alpha was reduced by -12.65 pg/ml in low corticosteroids group compared to the control group (p-value=0.0005).

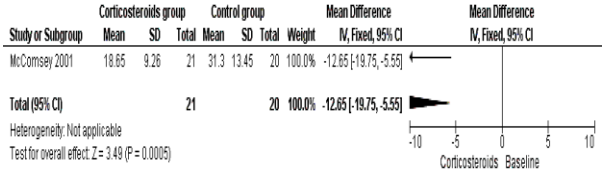

Figure 4: Forest plot of comparison: corticosteroids group versus baseline data, outcome: Plasma TNF-alpha (pg/ml) at 4 weeks.

TNF-alpha at 8 weeks: the calculated mean difference of plasma TNF-alpha at 8 weeks between low dose corticosteroids group and control was -9.72 [-16.61, -2.83] with p=0.006. We can conclude that the mean difference of TNF-alpha was reduced by -16.61 pg/ml in low corticosteroids group compared to the control group (p-value=0.006).

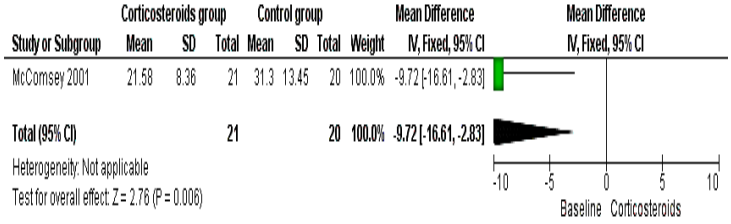

Figure 5: Forest plot of comparison: Corticosteroids versus baseline data; outcome: Plasma TNF-alpha (pg/ml) at 8 weeks.

Plasma Il-6 at 4 weeks: the calculated mean difference of plasma Il-6 at 4 weeks between low dose corticosteroids group and control was -0.62[-2.88, 1.64] with p=0.59. We can conclude that the mean difference of Il-6 was reduced by -0.62 pg/ml in low corticosteroids group compared to the control group, therefore the results were not statistically significant.

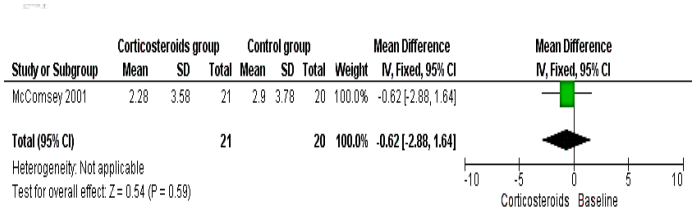

Figure 6: Forest plot of comparison: Corticosteroids versus baseline data; outcome: Plasma Il-6 level (pg/ml) at 4 weeks

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Plasma Il-6 at 8 weeks: the calculated mean difference of plasma Il-6 at 8 weeks between low dose corticosteroids group and control was -0.52[-2.67, 1.63] with p=0.64. Then, the Il-6 mean difference was reduced by -0.52 pg/ml in low corticosteroids group compared to the control group, therefore the results were not statistically significant.

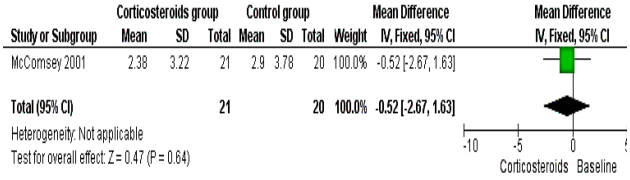

Figure 7: Forest plot of comparison: Corticosteroids versus baseline data; outcome: Plasma Il-6 level (pg/ml) at 4 weeks

Discussion

Based on the literature that was consulted, the level of evidence among the articles included in this review was considered as low to moderate evidence, because 2 RCTs were low risk of bias in general therefore 1 prospective cohort study and 1 trial were high risk of bias. However, the trial article classified as before and after the intervention did not include control groups to establish a comparison. The comparison was considered as the baseline results.

The RCTs were conducted as double-blinded studies, which is extremely important in understanding the clinical responses in this type of experimental design. However, to compare groups of patients who received CSs with control group (did not receive CSs) with the different outcomes: CD4 count, viral load, TNF-alpha and Plasma Il-6. However, because of the lack of studies in this, the authors considered 2 studies of low quality of evidence, increasing the level of bias. In general, these articles were considered to have few numbers of patients, which directly interferes with the evidence of the results. In addition, in the analyses of the 4 included studies performed, revealed the 95% CI means difference for respectively viral load and CD4 were large enough which imply that imprecision in these studies. Although 95% CI for CD4 was statistically significant, this imprecision limits the extrapolation of these results.

The authors observed that the percentages of heterogeneity were high in different meta-analysis. It is important to point out that this review included in 3 studies designs as mentioned above, furthermore, the participants were in different HIV stages, then the baseline CD4 count were different among studies. Lastly, two types of CSs were included in intervention groups (prednisone and prednisolone), this could be influence the large heterogeneity observed in meta-analysis.

McComey 2001 was the only study that reported clearly TNF-alpha and Il-6 outcomes; the comparison between the control group and the CS group regarding TNF-alpha was statistically significant in 4 and 8 weeks with P = .0005 and .006 respectively. However, Il-6 was not statistically significant. These inflammatory could highlight the relationship between CSs and HIV disease progression; therefore more studies with rigorous study designs are needful in this field.

CSs have shown multiple uses in HIV positive patient, its uses in autoimmune hepatitis, polymyositis and Sjögren's syndrome (Kaku 2014), TB meningitis (Jiménez 2005) pneumocystis pneumonia (PCP) and cerebral toxoplasmosis (Grant 2015). However, the lack of strong evidence CSs on HIV disease progression did not imply its use. Thus, more clinical and controlled studies need to be designed to obtain data for strengthening this systematic review.

Conclusions

In conclusion, the administration of low dose CSs in HIV-infected patients could not be judged as ameliorating HIV disease progression. Low dose CSs could improve CD4 count, therefore the evidence was graded low. Serum TNF-alpha level was significantly decreased in low CSs group with moderate evidence, however this review was considered in context of many limitations. Then, more RCTs are needed to establish a clinical consensus.

Acknowledgements

We gratefully thank the whole review team for active contribution in different steps of this review.

Declarations of interest

Authors compelled no conflict of interest

Published notes

The study protocol was registered on Prospero as reference: Tamuzi Lukenze Jacques, Jonathan Tshimwanga Lukusa. Effect of low dose corticoids in HIV disease progression: systematic review. PROSPERO 2017:CRD42017054384 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054384

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