Table E.1.4.d.6: Effects of physical activity on viral load and CD4+ cell count among people living with HIV

Questions: What is the association between physical activity and disease progression? Is there a dose response association (volume, duration, frequency, intensity)? Does the association vary by type or domain of PA?
Population: People living with HIV
Exposure: Greater volume, duration, frequency, or intensity of physical activity
Comparison: No physical activity or lesser volume, duration, frequency, or intensity of physical activity
Outcome: Markers of disease progression (CD4 count, CD4 percentage, viral load)

Exercise modality	Study	No. of Studies No. of participants	AMSTAR 2 Score	GRADE CRITERIA					Summary of findings	CERTAINTY
				Risk of Bias	Inconsis-tency	Imprecision	Indirectness	Publication Bias		
Aerobic Exercise	Nixon, 2005 *(70)*	10 RCTs, N=276	High	Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No publication bias	All ten included studies reported immunological/virological outcomes with a total of 276 participants aged between 18 and 58 years. The $CD4^+$ cell count of the participants ranged from <100 to greater than 1000 cells/mm^3, and women comprised less than 15% of the total number of participants. Meta-analysis showed no difference in $CD4^+$ cell count for participants in the exercise intervention groups compared to the non-exercising control groups (Weighted Mean Difference: 14.3 cells/mm^3, 95% CI: -25.8, 54.5, n=209, p=0.48) (Baigis 2002; LaPerriere 1990; Lox 1995; Perna 1999; Smith 2001; Stringer 1998). Meta-analysis also showed no difference in $CD4^+$ percentage for participants in the exercise interventions groups compared to the non-exercising control groups (Weighted Mean Difference: -0.2%, 95% CI: -3.1, 2.7, n=118, p=0.90) (Baigis 2002; Smith 2001). Meta-analysis demonstrated no difference in viral load for participants in the exercise intervention groups compared to the non-exercising control groups (Weighted Mean Difference: 0.40 log10 copies, 95% CI: -0.3, 1.1, n=63, p=0.25) (Smith 2001; Stringer 1998).	LOW (no effect)
	O'Brien, 2004 *(73)*	10 RCTs, N=458 HIV+ only participants	high	Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	Serious publication bias	All ten studies included used $CD4^+$ cell count as an outcome. Participants were aged between 18 and 58 years and their $CD4^+$ cell count ranged from <100 to greater than 1000 cells/mm^3, with women comprising less than 15% of the total number of participants. Five meta-analyses showed no difference in $CD4^+$ cell count for participants in any type of aerobic exercise intervention group compared with the non-exercising control group (weighted mean difference: 14 cells·mm^{-3} , 95% CI: -26, 54, N= 209), no difference in $CD4^+$ cell count of participants in the constant aerobic exercise group compared with non-exercising control group (weighted mean difference: -4 cells·mm^{-3} , 95% CI: -50, 42, N	LOW (no effect)

									164) and non-significant improvement in $CD4^+$ cell count of 70 cells·mm^{-3} (95% CI: -11, 151, N 45) for participants in the interval aerobic exercise group compared with the non-exercising control group. Although not statistically significant, the point estimate was above 50 cells·mm^{-3}, which represents a possible clinically important increase in $CD4^+$ cell count. There was no difference in $CD4^+$ cell count in the moderate intensity aerobic exercise group compared with the heavy-intensity exercise group (weighted mean difference: -34, 95% CI: -156, 89, N 39) and no difference in $CD4^+$ cell count for participants in the combined aerobic and progressive resistive exercise group compared with non-exercising control group (weighted mean difference: 6 cells·mm-3, 95% CI: -71, 83, N 46). Meta-analysis of three studies showed no difference in viral load for participants in the exercise intervention groups compared with the non-exercising control groups (weighted mean difference: 0.40 log10 copies, 95% CI: -0.28, 1.07, N 63).	
	O'Brien, 2016 *(67)*	24 RCTs, N=1242	high	Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	Serious publication bias	Twenty-four studies with 936 participants (at study completion), who were mostly male, taking ART (19 studies) were included in the review. Seven meta-analyses showed non-statistically significant changes in CD4+ cell count between comparison groups. Results showed a trend towards an increase in CD4+ cell count for participants in the aerobic or combined aerobic and PRE intervention group compared with the non-exercising control group; constant or PRE compared with no exercise; and a significant increase in CD4+ cell count for interval aerobic exercise compared with no exercise. The point estimate in the latter two meta-analyses was above 50 cells/mm3, which suggests a trend towards a potentially clinically important improvement in CD4+ cell count among exercisers compared with non-exercisers. Meta-analyses showed no difference in CD4+ cell count for constant or interval aerobic exercise compared with no exercise; constant aerobic exercise compared with no exercise; as well as combined aerobic exercise and diet and/or nutrition counselling group compared with diet and/or nutrition counselling. No difference in CD4+ cell count was found for participants exercising at moderate compared to heavy intensity exercise. Four meta-analyses showed no difference in viral load	MODERATE (no effect)

									for participants in the aerobic exercise intervention group compared with the non-exercising control group, as well as the constant aerobic exercise group compared with the non-exercising control group; no difference in the combined aerobic and PRE group compared with the non-exercising control group; and no difference for participants in the aerobic or combined aerobic and PRE intervention group compared with the non-exercising control group.	
	O'Brien, 2010 *(69)*	14 RCTs, N=454	high	**$CD4^+$ cell count**					Five meta-analyses showed no significant change in $CD4^+$ cell count between exercise and no exercise groups.	MODERATE (no effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias		
				CD4 Percentage					Two meta-analyses demonstrated no difference in $CD4^+$ percentage for participants in the exercise intervention group compared with the non-exercising control group, as well as the constant aerobic exercise group compared with the non-exercising control group (WMD: -0.33%, 95% CI: -1.98, 1.32, n=118, *P*=0.69) (Smith, 2001, Baigis, 2002).	High (no effect)
				No serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias		
				Viral Load					Three meta-analyses demonstrated no difference in viral load for participants in the exercise intervention group compared with the non-exercising control group, as well as the constant aerobic exercise group compared with the non-exercising control group (WMD: 0.40 log10copies, 95% CI: -0.28, 1.07, n=63, *P*=0.25) (Smith, 2001; Stringer, 1998), and no difference in the combined aerobic and PRE	HIGH (no effect)

				No serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias	group compared with the non-exercising control group (WMD: 0.31 log10copies, 95% CI: -0.13, 0.74, n=60, *P*=0.17) (Grinspoon, 2000, Dolan, 2006).	
Resistance Exercise	Poton, 2016 *(78)*	13 RCTs, N=291	moderate	No serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias	The review included a total of 291 participants and 43.1% were female. A slight increase in $CD4^+$ cell count occurred with an overall effect size of 0.37 (0.13–0.61; P = 0.003; ~26.1%).	MODERATE (+ve effect)
	O'Brien, 2017 *(72)*	20 RCTs, N=764	high	**CD4 count**					Two meta-analyses demonstrated no statistically significant changes in $CD4^+$ cell count between comparison groups, one demonstrated a significant increase in $CD4^+$ cell count favouring exercise, and the other demonstrated a significant decrease in $CD4^+$ cell count favouring testosterone alone. Point estimates were >50 cells/mm^3 for two meta-analyses comparing exercise to control, which suggested a positive trend towards a potentially clinically important improvement in $CD4^+$ cell count with exercise compared to no exercise.	VERY LOW (+ve effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias		
				Viral load					Three meta-analyses demonstrated no difference in viral load for participants in the combined PRE and aerobic exercise intervention group compared with the non-exercising control group, as well as the combined PRE and aerobic exercise group with diet and/or nutrition compared with the non-exercising diet and/or nutrition only group. None of the meta-analyses were significant for heterogeneity.	MODERATE (no effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias		
	O'Brien, 2008 (*74)*	10 RCTs, N=332	high	Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	The review included a total of 332 participants, whose age ranged from 18 - 66 years. Their CD4 counts ranged from under 100 to greater than 1000 cells/ mm^3. Less than 30% of the participants were women (87/332 participants). Three meta-analyses showed no difference in $CD4^+$ cell count for participants in the combined aerobic and PRE group compared to the non-exercising control group (WMD: 24.83 cells/mm3; 95% CI: -23.70, 73.36; p = 0.32; n = 84) and for participants in the PRE or combined PRE and aerobic exercise group compared to the non-exercising control group (WMD: 38.51 cells/mm3; 95% CI: -7.54, 84.56; p = 0.10; n = 106). A significant decrease in CD4+ cell	LOW (no effect)

									count was found in the combined PRE plus testosterone or combined PRE and aerobic exercise plus testosterone group compared with the testosterone only group (WMD: -32.13 cells/mm3 ; 95% CI: -56.96, -7.30; p = 0.01; n = 51). These results did not reach the authors' pre-specified threshold for clinical importance (50 cells/mm3). One meta-analysis demonstrated no difference in viral load among participants in the combined PRE and aerobic exercise group compared with the non-exercising control group (WMD: 0.31 log10 copies; 95% CI: -0.13; 0.74; p = 0.17; n = 60). Individual studies also showed no difference in viral load among exercisers compared with non-exercisers.	
Multimodal Exercise	Ibeneme, 2019b *(65)*	19 RCTs, N=661 participants included for QoL.	high	Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias	Farinatti (2010) reported no significant change in the $CD4^+$ cell count in either the exercise group or the control group. The exercise group (n = 19) were involved in aerobic training (cycle ergometer) for 30 min of moderate intensity, strengthening exercise (2 sets of 12 repetitions of 5 exercises at 60–80% 12 Repetition Maximum) for 50 min and flexibility exercise (2 sets of 30s at maximum range of motion of 8 exercises) while the control group (n = 8) received no treatment. The study reported no significant change in the CD4 T-cell count in either the exercise group or the control group (p = 0.19 for CD4 T-cells and p = 0.22 for CD4 %).	MODERATE (no effect)
	Pedro, 2017 *(72)*	5 RCTs, N=253	high	No serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	CD4 cell count was not influenced by physical training.	MODERATE (no effect)

Abbreviations:; PICO = population, intervention, comparator, outcome;; RoB = risk of bias; RCTs = randomised controlled trials

1. O'Brien 2016: The authors reported a MODERATE grade for CD4+ cell count and did not report for viral load. CD4+ cell count was assigned a MODERATE GRADE due to incomplete outcome data (withdrawals of included studies were >15 %). We also assigned a MODERATE GRADE for viral load due to attrition bias and performance bias in the review.

2. O'Brien, 2010

   - CD4 cell count: Downgraded to MODERATE due to heterogeneity in the included studies.
   - CD4 Percentage: HIGH, no reason to downgrade even if RoB is unclear.
   - Viral Load: HIGH, no reason to downgrade even if RoB is unclear.

3. O'Brien, 2004: Downgraded to LOW because the authors report a possibility of publication bias, there was also attrition bias (20% drop out in 6 studies and more than 50% dropout in 2 studies), the review is also based on a small number of trials and participants. Heterogeneity may have occurred due to a variety of exercise interventions being used.

4. O'Brien, 2008: Downgraded to LOW because of a lot of variation among individual studies in the types of interventions, participants and outcomes, which may have led to heterogeneity and Indirectness. Also, there is RoB due to attrition bias because of high withdrawal rates (>15%). There was also lack of blinding to the PRE intervention which may have resulted in the Hawthorn effect. The authors also report a possibility of performance bias due to increased levels of interaction between the investigators and participants in the exercise group resulting in more

favourable outcomes for exercisers compared to non-exercisers. The review also used a small number of studies (n = 10) and there was total outcome data not available for 69 (17%) participants.

5. Nixon, 2005: Downgraded to LOW due to (a) RoB due to attrition bias as a result of high withdrawal rates ranging from 4-76% (b) indirectness which may have been caused by the heterogeneity of outcome measures.

6. O'Brien, 2017

    - CD4 count: First downgraded to LOW because RoB due to a high risk of performance bias existing across the included studies since 85% of them lacked participant blinding to the exercise intervention. There was also a high risk of attrition bias as 555 of the included studies reported rates of withdrawal greater than 15%. Indirectness could have been caused by heterogeneity as it was reported to be present in 47% of the meta-analyses due to participant variability in ART use, body composition, comorbidity, gender, type and location of intervention and method of outcome measurement. For CD4 count the LOW grade was further downgraded to VERY LOW because for CD4 count, 3 of the 4 meta-analyses that were done were statistically significant for heterogeneity.
    - Viral load: The authors of the review graded the result as MODERATE because they were moderately confident in the non-significant effect estimate of 0.12 log10copies demonstrating no difference in change in viral load comparing PRE exercise (or combined PRE and aerobic exercise). This outcome was downgraded from HIGH to MODERATE GRADE quality of evidence due to incomplete outcome data (withdrawals of included studies were >15%).

7. Poton, 2017: Downgraded to MODERATE because we are uncertain about the status of RoB, inconsistency and imprecision as there insufficient information about these in the review.

8. Pedro, 2017: Downgraded to MODERATE due to indirectness which might have been caused by different type of individuals in different studies, different types of exercise interventions and different types of assessment methods.