Metformin for reversal of accelerated biological aging in persons with HIV: a pilot clinical trial

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BACKGROUND

There is interest in **metformin** as a drug to **delay aging** in the general population. This is **the first trial** to evaluate the impact of metformin on biological aging measured by epigenetic clocks with prognostic value in PHW.

METHODS

Phase II randomized 1:1, double-blind, pilot clinical trial comparing metformin 850mg BID (850mg QD in participants treated with dolutegravir) vs placebo.

Inclusion criteria:

- Age ≥ 50
- HIV viral load < 50 for ≥ 1 year and CD4 > 500
- HOMA-IR ≤ 2.6
- BMI <30
- Normal B12 vitamin levels

Exclusion criteria:

- Diabetes
- Stroke, heart failure, dementia, cancer or renal impairment
- Pregnancy.

Objectives were to assess **metformin safety**, **changes in Epigenetic Age Acceleration** (EAA) measured by Horvath, Hannum, PhenoAge, GrimAge, and DNAmFitAge epigenetic clocks in whole blood, and **changes in blood telomere length measured by DNA methylation** (DNAmTL) after 96 weeks of follow-up. EAA was defined as the residuals from the regression of epigenetic age on chronological age. Changes between treatment groups were analyzed using linear mixed models with random intercepts and slopes, and Wilcoxon rank-sum test.

RESULTS

40 participants, of whom **35** (17 metformin and 18 placebo) maintained their randomized treatment until week 96.

At baseline, **groups were balanced (Table 1)** without differences in EAA measures or DNAmTL. **Discontinuations from study were not attributed to adverse events related to the study medication**

Participants receiving metformin demonstrated a significant increase in serum GDF15, a biomarker associated with metformin adherence.

In PWH without diabetes metformin is safe, well-tolerated and has a potential positive biological effect on DNA methylation-based telomere length

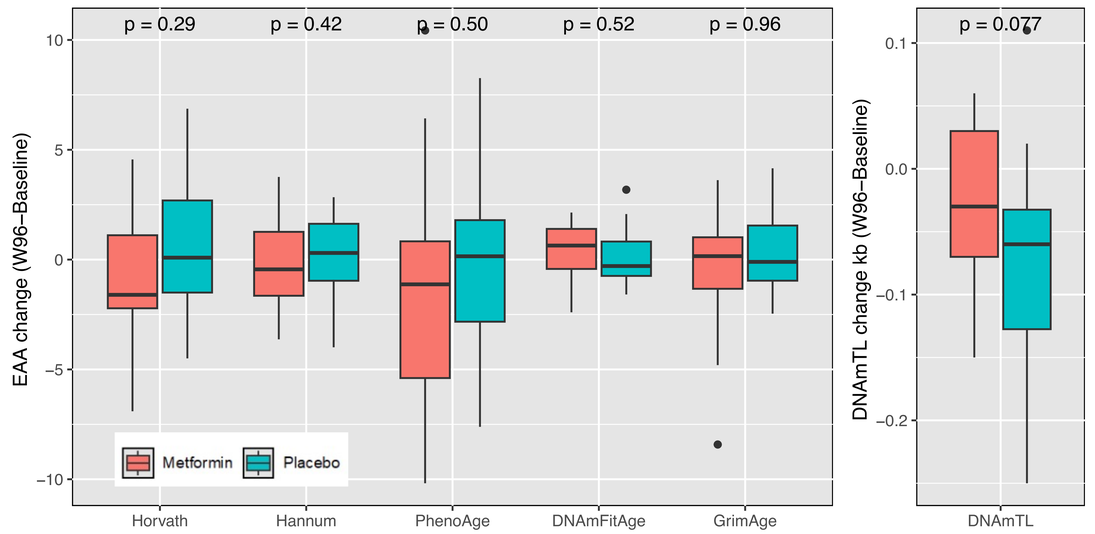


Figure 2. Changes in EAA measurements and DNAmTL after 96 weeks of follow-up . Boxes show medians and IQRs; whiskers correspond to 10th and 90th percentiles. P-values shown are Wilcoxon rank-sum test.

	All N* = 35	Metformin N = 17	Placebo N = 18
Chronological age	57 [53.1;61,1]	56.8 [52.4;64.8]	57.8 [53.6;59.9]
Female	10 (28.6%)	6 (35.3%)	4 (22.2%)
BMI	24.8 [23,1;25.7]	24.4 [23.1;25.3]	24.8 [22.6;26.1]
HOMA-IR	1.3 [1.0;1.9]	1.4 [1.2;1.9]	1.3 [0.9;1.7]
Nadir CD4	307.5 [156.2;393.2]	311 [91;350]	304 [200;428]
Current CD4	824.5 [621;985.5]	819 [608;961.5]	830 [643;1002]
CD4/CD8	1.3 [0.9;1.6]	1.1 [0.8;2.1]	1.3 [1;1.5]
Dolutegravir (%)	23 (65.7)	10 (58.8)	13 (72.2)

Table 1. Characteristics of participants.

*N =those who mantained randomized treatment until week 96. Quantitative variables are expressed as medians and interquartile range.

RESULTS

Table 2.Safety Summary

	Metformin N = 19 *	Placebo N = 21 *
Any AE	33	37
TRAEs	1	1
Grade 1 and 2	1	1
Grade 3 and 4	0	0
Serious AEs	0	1
Serious TRAEs	0	0
AE leading to study discontinuation	0	1
TRAE leading to discontinuation	0	1

AE: Adverse Events TRAEs: Treatment-Related Adverse Events
*N = all randomized partipants. Total 40

At week 96, there were **no significant differences between groups in CD4 counts, glomerular filtration rate CDK-EPI, liver enzymes, and all participants remained virologically suppressed.** More details about safety are shown in Table 2.

EAA and DNAmTL changes are shown in figure 2. Median decreases in EAA were observed in Horvath, Hannum and PhenoAge clocks, without statistically significant differences. A trend towards a **potential effect on DNAmTL was observed.** Linear mixed models showed a similar evolution between groups in EAA and DNAmTL.

CONCLUSIONS

In this pilot trial, metformin treatment for 96 weeks **was safe and well-tolerated** in PWH without diabetes. While no trend favoring metformin was observed across the epigenetic clocks analyzed, **the trend in DNAmTL suggests a potential positive biological effect**, warranting further investigation in larger studies.

ADDITIONAL INFORMATION

Visit poster 867 and our oral abstract presentation on Wed 12th, at 10:00 AM in the Cardiometabolic Complications and Aging session

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