



Metformin Decreases Weight and Inflammation in Non-Diabetic People Living with HIV: Link with Microbiota Composition

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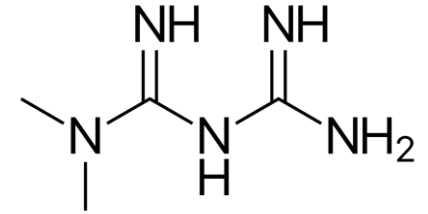
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Conflict of Interest Disclosure: I have no conflicts of interest



Metformin

- **Anti-diabetic:** prevents hyperglycemia without inducing hypoglycemia
- **Anti-inflammatory** in animal models and in obese and diabetic people
- **Anti-aging** in animal models



Metformin's activity is dependent on the **presence of a microbiota** in animal models and modifies the gut microbiota composition in diabetic and healthy people.

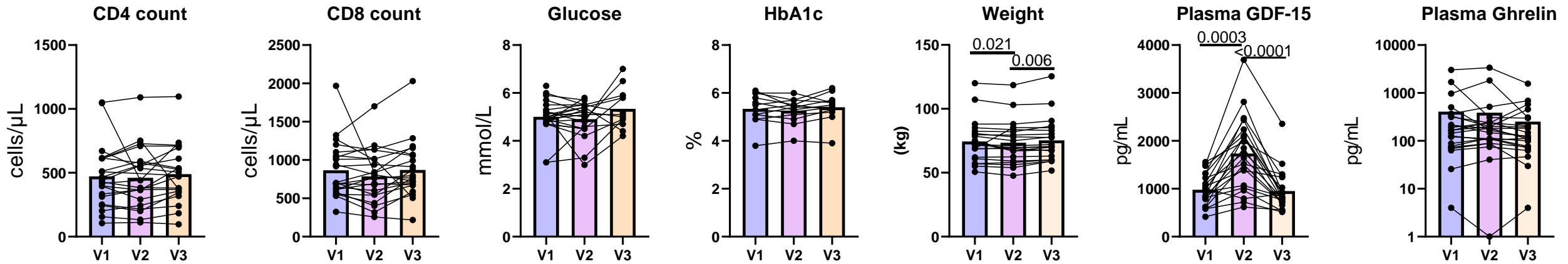
Hypothesis: Metformin will decrease inflammation and weight in people living with HIV (PLWH), in association with gut microbiota modification.

CIHR CTN LILAC study: 22 PLWH under antiretroviral therapy for more than 2 years with undetectable viremia and a CD4/CD8 ratio <0.7 to select people with high risk of inflammation were invited to take metformin daily for 12 weeks, and then stop for 12 more weeks. Blood and stools were collected at baseline, after metformin treatment, and after its discontinuation.

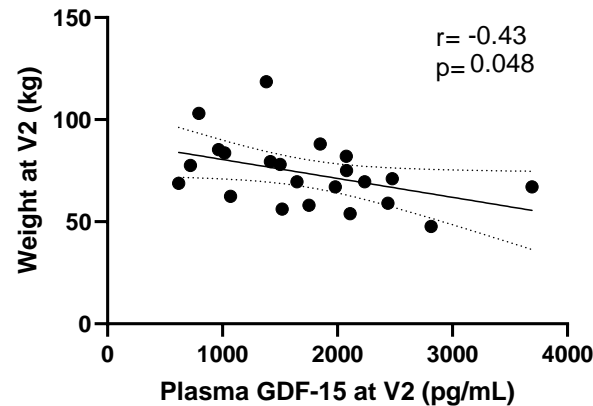
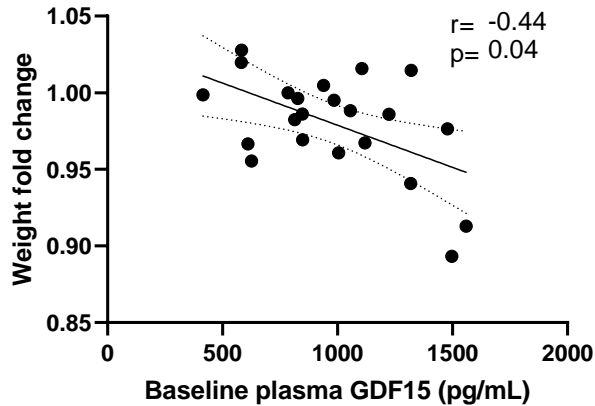
Microbiota composition was analyzed by 16S rRNA gene sequencing in stools. GDF-15, Ghrelin and inflammatory markers sCD14 were quantified in plasma by ELISA. Serum levels of short chain fatty acids were assessed by LC-MS.



Clinical measurement



V1 = baseline, V2 = after 12 weeks of metformin, V3 = 12 weeks after metformin discontinuation



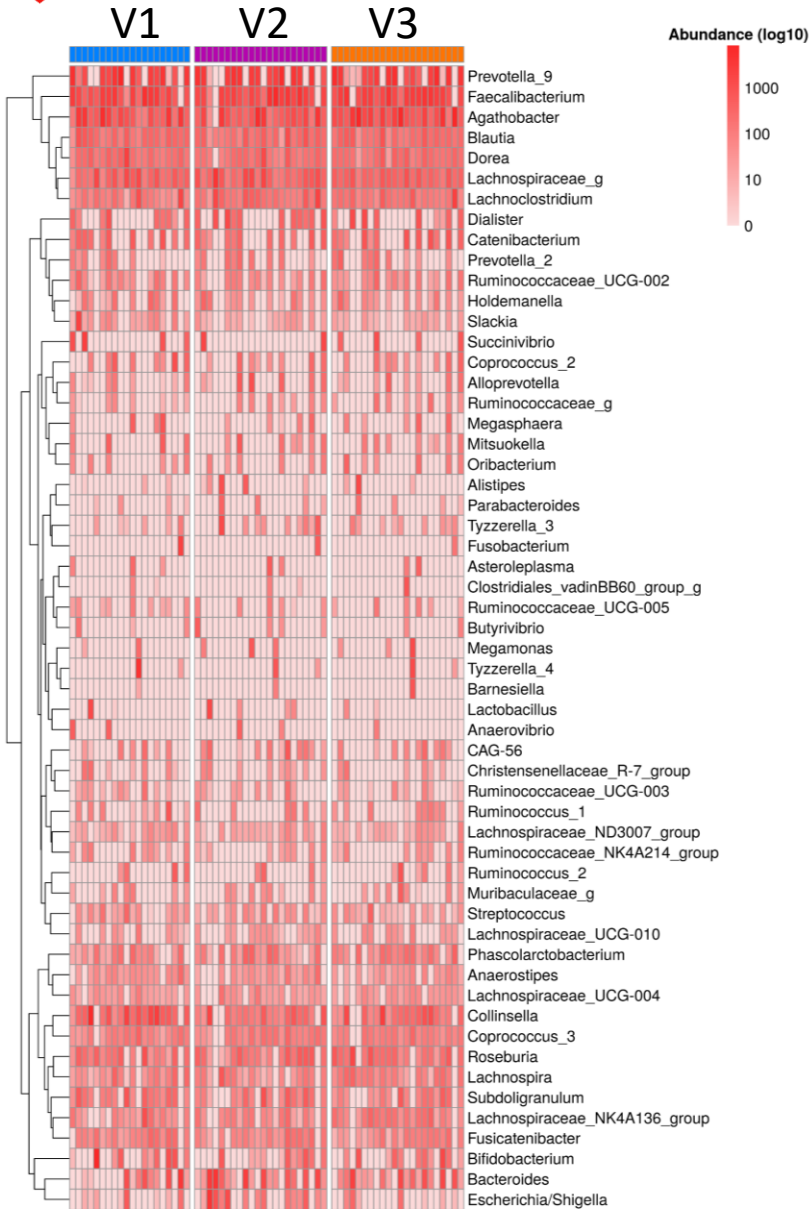
12 weeks of metformin didn't induce significant variation in CD4 or CD8 count, glucose level nor %HbA1c in our participants.

However, we observed a **weight loss (median 1.6 kg)** in our participants, concomitant with an **increase in plasma levels of the growth factor GDF-15 after metformin treatment**. Levels of at GDF-15 at baseline and after metformin treatment correlated with weight loss.

The other anti-hunger hormone Ghrelin was not affected by metformin intake.



Microbiota and inflammation



Compared to baseline, metformin treatment:

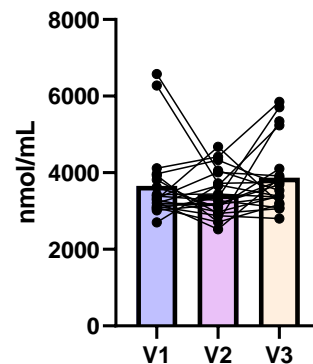
- **Decreased *Collinsella*** abundance
- **Increased *Escherichia_Shigella*** and ***Lachnospiraceae*** abundances

After metformin discontinuation:

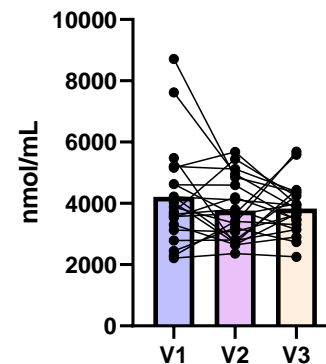
- Abundance of ***Escherichia_Shigella*** went back to baseline levels.
- Abundance of ***Lachnospiraceae_NK4A136_group*** was increased.

Lachnospiraceae and ***Lachnospiraceae*** bacteria are producers of the **anti-inflammatory short chain fatty acid butyric acid**, which levels were **increased after metformin discontinuation**. Concomitantly, plasma levels of the inflammatory marker **sCD14** were **decreased** after metformin discontinuation.

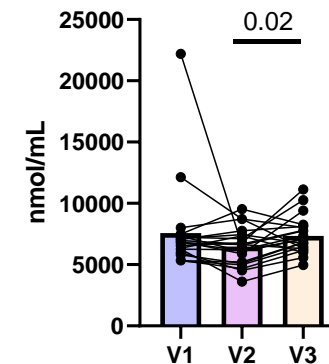
Serum Propionic acid



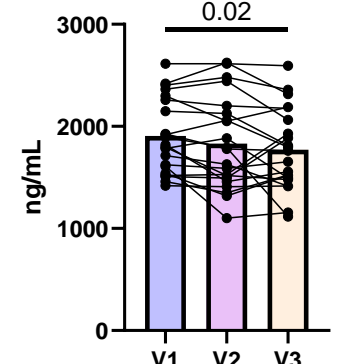
Serum Succinic acid



Serum Butyric acid



Plasma sCD14





12 weeks of metformin treatment in ART-treated PLWH:

- Appeared **safe**.
- Decreased participant **weight**, in a **GDF-15 dependant manner**, as it was previously seen in diabetic people.
- Slightly **modify the gut microbiota** composition, similarly to what was observed in diabetic people or healthy men.
- Increased abundance of **butyric acid-producing bacteria**, and serum butyric acids levels, mostly after metformin discontinuation.
- Concomittantly, levels of the **inflammatory marker sCD14** were **slightly decreased** after metformin intake.

As metformin was well tolerated, a longer treatment will be needed to confirm the effect observed in our study.

→ **Combination of ART and metformin might decrease inflammation markers and decrease risks of non-AIDS comorbidities in PLWH.**