HIV and Antiretrovirals have unique in vivo effects on insulin resistance in HIV

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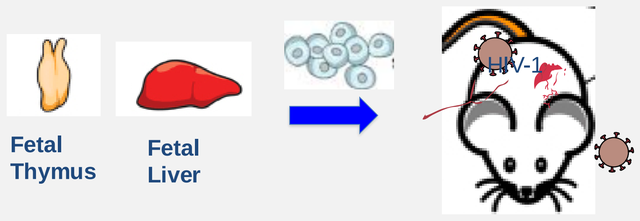
BACKGROUND

Diabetes mellitus (DM) is more common in antiretroviral drug-treated (ART) people with HIV (PWH) compared with people without HIV(PWOH), even without obesity. Emerging epidemiologic data suggests that PWH not on ART has a lower DM risk than PWOH. We have shown that measures of pancreatic beta cell function were higher (i.e., better function) and markers of beta cell stress were lower (i.e., reduced stress) in ART-naive PWH compared with ART-treated PWH and PWOH in Page 2 | 3 PWH who have not initiated ART (PMID: 35134838). However, in vivo data on the role of HIV-1 per se versus ART in chronic HIV infection are lacking because observational human studies cannot dissect the differential effect of HIV-1 versus ART on signatures of insulin resistance (IR) in tissues not readily accessible. To address these gaps in knowledge, we used a mechanistic humanized mouse model of chronic HIV infection to dissect in vivo the direct impact of HIV-1 versus ART on IR

OBJECTIVES

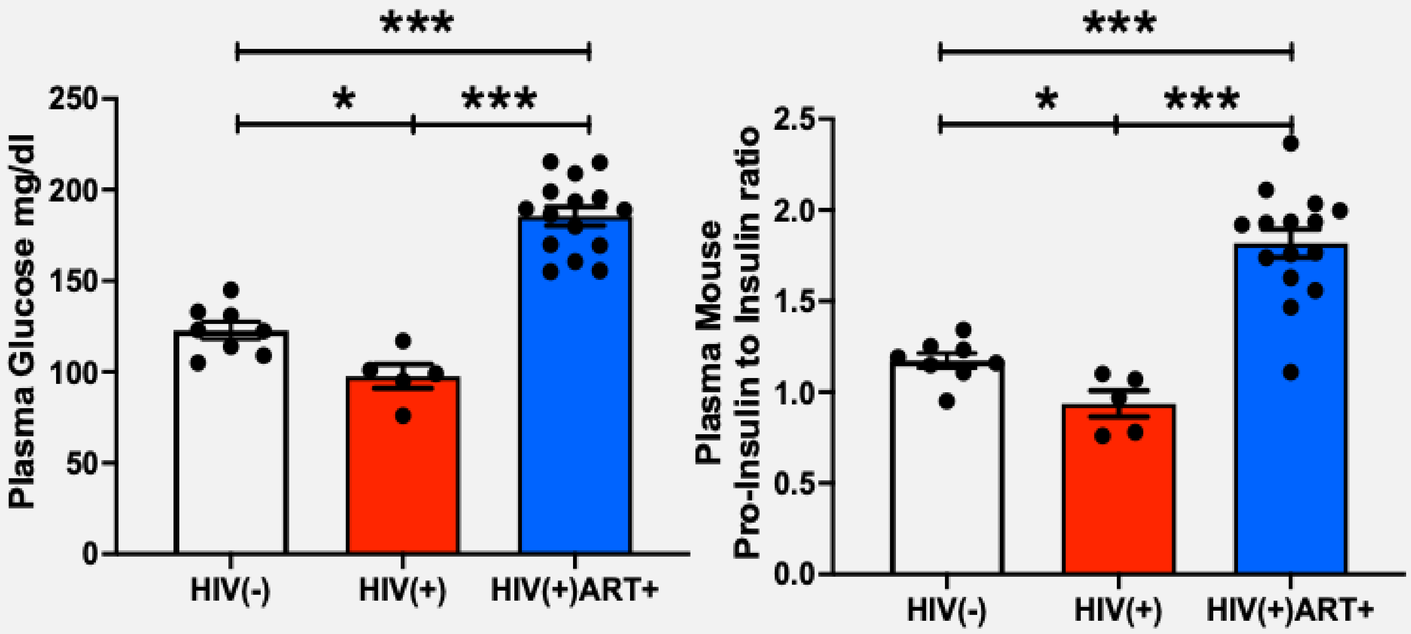
To dissect in vivo the direct impact of HIV-1 versus ART in the pathogenesis of insulin resistance using a physiologically relevant humanized mouse model of HIV infection.

METHODS



TKO C57Bl6 humanized mice that are not prone to Graft versus Host disease (GVHD), were infected with HIV-1 (that infects only human immune cells) and treated with FTC/TDF/RAL (that impacts both mouse and human cells) for 3 months, as previously (PMID: 33306550). Plasma glucose, insulin (I), proinsulin (pro-I) and Pro-I to I ratio (high ratio indicates IR) were determined in the plasma of mice from 3 groups: A) HIV uninfected (HIV-, n=8), B) HIV+: HIV-1 viremic not on ART (n=5), C: infected but treated with ART (HIV+/ART+, n=15).

RESULTS



- Compared to HIV- mice, HIV-1 consistently tended to decrease plasma glucose levels ($p=0.07$) and reduced plasma levels of the mouse (m) insulin (I), Pro-I, and Pro-I/I ratio ($p<0.05$ for all comparisons).
- Compared to HIV+ and HIV- mice, ART per se in the HIV+/ART+ mice increased plasma levels of glucose, I, Pro-I, and Pro- I/I ratio ($p<0.05$ for all comparisons) (Figure).

CONCLUSIONS

- Our study dissected in vivo complex effects of HIV-1 per se versus ART on IR in vivo.
- We confirmed that HIV-1 per re reduces rather than increases IR in vivo.
- We have hypothesized that the protective effect against DM may be related to the inherent immune dysregulation associated with untreated HIV. ART rather than HIV increased IR and compromised murine pancreatic beta cell function.
- Large longitudinal studies of PWH with molecular signatures of immune dysregulation and IR before and after ART initiation are needed to clarify further the role of HIV, ART, and immune dysregulation on diabetes mellitus in PWH.

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