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Proteomic Profiling Identifies CLPP Associated with INSTI-Induced Weight Gain in People with HIV

Xin Huang[1], Fada Wang[1], Liyuan Zheng[1], Ziyan Wang[1], Leidan Zhang[1], Taisheng Li[1],Wei Cao[1#]

[1]Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China

BACKGROUND

The use of integrase strand transfer inhibitors (INSTI) is associated with weight gain, but the underlying mechanisms remain unclear. This study aims to compare the plasma proteomic alterations in people with HIV (PWH) who experienced different weight trends after using INSTIs, and to identify critical factors in INSTI-induced weight gain.

METHODS

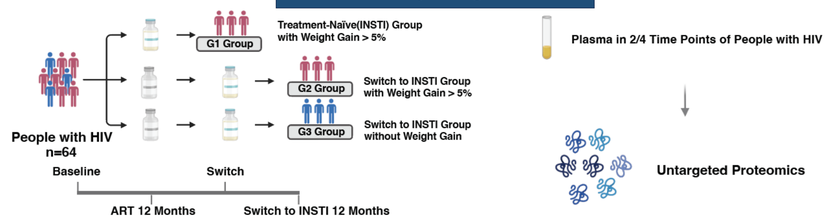
A total of 64 PWH were recruited and stratified based on their therapeutic history and weight changes over the first year (G1 receiving INSTI with weight gain > 5%; G2 switching to INSTI with weight gain > 5%; and G3 switching to INSTI without weight gain > 5%). Plasma samples underwent longitudinal untargeted proteomic analysis; paired t-tests were used for within-group temporal comparisons. Concurrently, random forest models based on top 30 differential proteins (G1+G2 vs G3, t-test) were constructed to predict weight gain status, with performance assessed by out-of-bag error.

RESULTS

The weight-stable group G3 showed no significant proteomic changes 12 months post-switching, confirming that switching to INSTI alone did not induce widespread proteomic drift. In contrast, the treatment-naïve group G1 displayed the most extensive remodeling reflecting immune recovery, while the switch-weight-gain group G2 exhibited significant perturbations distinct from the stable control. Since G3 showed no significant differences, to isolate robust biological drivers of obesity from cohort-specific background noise, we cross-referenced candidate proteins from G2 with those from the naïve cohort. We identified a robust signature of 18 core proteins that displayed consistent upregulation or downregulation across both weight-gaining groups (G1 and G2). Specifically, mitochondrial and metabolic regulators such as CLPP and PPA2 were consistently upregulated. Finally, a random forest model was built using the top 30 differential proteins (pre-INSTI G1+G2 vs G3) to predict weight gain, with variable importance ranked by Mean Decrease Accuracy. The top 20 features were identified as core biomarkers, with KRT72 and KRT79 showing the highest importance, indicating their potential as primary drivers of weight gain susceptibility.

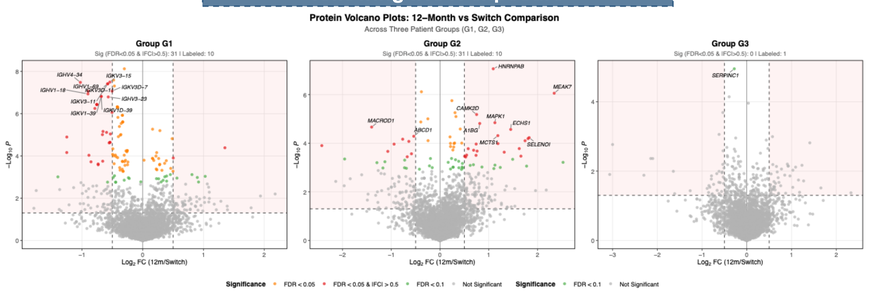
Proteomic identification of biomarkers for INSTI-associated weight gain.

Study Design

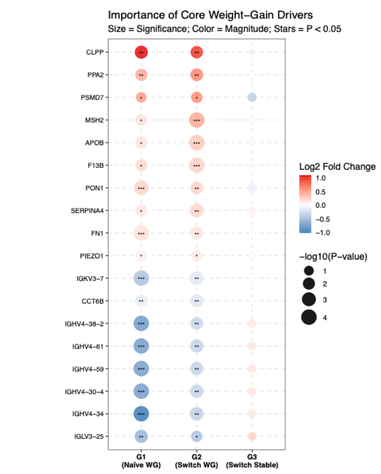


Results

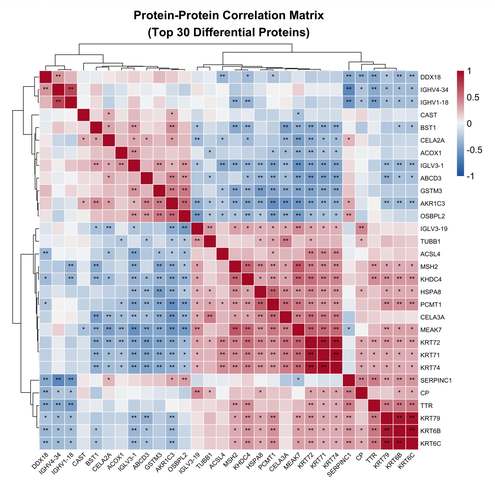
Group-specific proteomic trajectories following INSTI exposure



Mitochondrial and metabolic regulators show consistent upregulation in weight-gainers

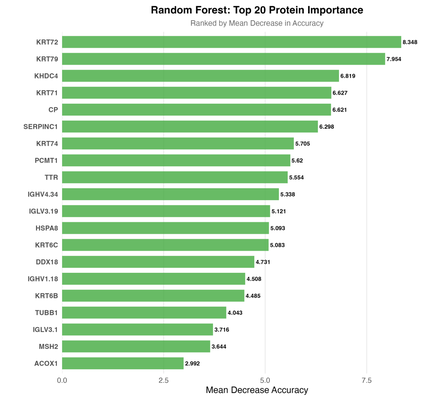


Correlation network reveals co-regulated protein modules in weight gain susceptibility



Results

Proteomic predictors of INSTI-associated weight gain



CONCLUSIONS

This study demonstrates that INSTI-associated weight gain reflects pre-existing susceptibility, as evidenced by proteomic stability in weight-stable switchers versus extensive remodeling in weight-gainers. We identified core proteins, including mitochondrial regulator CLPP, showing consistent dysregulation across weight-gaining cohorts. KRT72 and KRT79 emerged as top pre-INSTI predictors, providing mechanistic insights into obesity susceptibility and a foundation for pre-treatment risk stratification in PWH.

ADDITIONAL KEY INFORMATION

Author Contact Information
#Corrsepondence to:
Wei Cao, *MD*
Department of Infectious Diseases, Peking Union Medical Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No.1 Shuaifuyuan, Dongcheng District, Beijing, 100730, China.
E-mail address: wcao_pumch@163.com

PLAIN LANGUAGE SUMMARY

We demonstrate that INSTI-associated weight gain stems from pre-existing metabolic susceptibility, and identify core proteins (including mitochondrial regulator CLPP) and pre-INSTI biomarkers KRT72/KRT79 through proteomics that enable pre-treatment risk prediction and personalized ART selection.