Untangling the causal ties between antiretrovirals and obesity

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Weight gain and clinical obesity are common complications of HIV treatment with modern antiretroviral therapy (ART) regimens.[1–5] Although several potential drivers of treatment-emergent obesity have been proposed, a fundamental question remains about whether modern ART induces regain of bodyweight for those who lost weight after infection and before starting therapy, or whether ART regimens directly cause excess bodyweight gain (figure).

No scientific study design is likely to directly resolve this question in humans, because a control group of individuals without HIV, unburdened by residual confounding, is likely to be elusive. However, in *The Lancet HIV*, Nikos Pantazis and colleagues[6] creatively consider a unique population in which to explore this question: individuals with recent HIV infection. They define this population based on a negative HIV test within the previous 12 months before HIV diagnosis. As the authors state, previous studies have often observed individuals with advanced HIV or HIV of indeterminant duration, making it difficult to know whether the bodyweight gain once ART begins is due to a return to health or a more direct obesogenic effect of ART itself.

The authors observed significant weight gain in a large, robust, longitudinal cohort of over 5000 adults who initiated ART within 12 months of a documented seroconversion. Bodyweight changes were measured from the time of ART initiation and followed up to the date of data extraction or regimen change. In adjusted models, people gained an average of 1–5 kg of bodyweight after ART initiation. Modestly larger gains were seen among women, people originating from sub-Saharan Africa, and those taking tenofovir alafenamide-containing regimens or integrase strand transfer inhibitor (INSTI)-containing regimens. For example, in an individual with a BMI at ART initiation of 18·5–24·9 kg/m², the estimated bodyweight gain after starting tenofovir alafenamide plus INSTI at 6 months was 2·39 kg (95% CI 1·91–2·87) and at 36 months was 4·76 kg (4·05–5·46), compared with 0·90 kg (0·48–1·31) and 1·98 kg (1·54–2·41) for those starting a non-nucleoside reverse transcriptase-containing regimen.[6] There are many strengths to this study; most notably a large sample size of people with a recent seroconversion date, robust modelling methods, and careful attention to measured confounders.

As in all large observational cohort studies, the analysis was also subject to limitations. Almost half as many of those who were included (n=5968) were excluded (n=2429) because of missing height or bodyweight data. Although the authors helpfully show that those with missing data were similar in terms of demographics, one could imagine a risk for selection bias. For example, if healthier patients (a designation which can be difficult to capture) were less likely to receive vital sign measurements at the time of ART initiation, and also less likely to have lost weight after HIV infection, this could have a substantial impact on the findings. The authors also estimated bodyweight changes at 3 years after ART initiation, even though the median observation time was less than 2 years. This might lead to extrapolation of inferences to timepoints beyond what is available for most of the study population. Finally, the study population was predominantly White men who have sex with men from Europe and North America, and generalisability should be interpreted within that context.

Perhaps most importantly, Pantazis and colleagues' study stops short of proving a causal relationship between ART and excess bodyweight gain. We suggest three primary reasons for this. First, as mentioned, there is no ideal control group for studies of ART and bodyweight gain. Overweight and obesity are common in the general population and whether the bodyweight gain observed in this study was excessive, as the authors suggest, expected, or even less than what would be

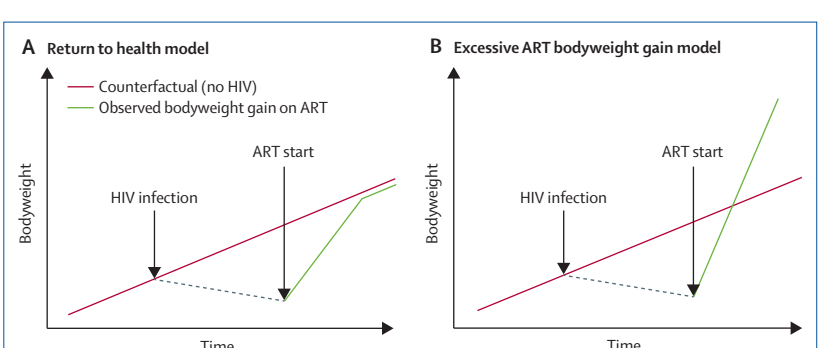

Figure: **Theoretical trajectories of bodyweight gain among people taking ART for HIV**
(A) Return to health model in which ART promotes bodyweight gain to restore health. (B) Excessive bodyweight gain model, in which ART or leads directly to excessive weight gain. ART=antiretroviral therapy.

expected in an HIV-uninfected population cannot be deduced with certainty.

Second, CD4 counts at initiation in this study (median 459 cells per µL [IQR 328–620]) were substantially lower than what would be expected in a population of people without HIV. This finding might be explained by the fact that even very early HIV infection is not a state of normal health. Indeed, in case series of acute HIV, bodyweight loss is among the commonly reported findings in approximately half of individuals.[7,8] A stronger argument for a causal effect of ART on bodyweight gain might be made in this case if bodyweight changes were modelled from the time of HIV infection; or stronger still, if they included bodyweight trajectories before HIV infection.

Finally, the trajectory of bodyweight gain after ART initiation also argues against a casual effect. The two-phased nature of the bodyweight gain reported in this study, with an initial phase of rapid bodyweight gain followed by a plateau, is common after ART initiation.[9] By contrast, if specific drugs were directly obesogenic, one would not necessarily expect a two-phase effect. Moreover, nearly all regimens assessed were associated with bodyweight gain. This argues against a drug-specific effect, as it seems unlikely that all antivirals would be associated with a similar obesogenic effect, given their varying mechanisms of action.

In summary, Pantazis and colleagues provide a novel approach to corroborating a substantial risk of bodyweight gain for people initiating modern ART. They convincingly redemonstrate that the magnitude of gain might vary by regimen and rightly conclude that bodyweight management strategies are urgently needed for people living with HIV on modern ART.[10] However, their analysis stops short of showing ART directly causes excess bodyweight gain. Unfortunately, the wait to answer that question might not ever be over.

We declare no competing interests

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