Aumento di peso nelle persone che vivono con HIV: ultimi aggiornamenti da CROI 2021.

Weight gain in people living with HIV: latest updates from CROI 2021.

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Riassunto

Con l'avvento della terapia antiretrovirale combinata (cART), il numero di persone che vivono con HIV (PCH) virosoppresse (HIV-RNA<50 copie/mL) è aumentato raggiungendo percentuali superiori al 90% nei paesi ad alto sviluppo economico, trasformando l'infezione da HIV in una patologia cronica. Vista l'elevata efficacia delle nuove terapie, la ricerca si sta concentrando nel migliorare la tollerabilità.

A questo proposito, un aspetto da approfondire è quello legato all'aumento di peso corporeo e dell'accumulo di grasso addominale, in particolare nelle PCH che assumono inibitori delle integrasi (INI). Questo può comportare un maggior rischio di sviluppare diabete mellito, sindrome metabolica e patologie cardiovascolari, rischio di per sé già aumentato nei PCH rispetto alle persone sieronegative. Diversi studi sono stati condotti sugli INI, ed in particolare sul dolutegravir a cui è stato imputato di causare un maggior aumento di peso rispetto agli altri farmaci.

Tuttavia, ci sono ancora molti aspetti da chiarire, fra cui i meccanismi fisiopatologici alla base dell'aumento di peso, le conseguenze per la salute e fattori predittivi di aumento di peso.

In questo contesto, al CROI 2021 sono stati presentati diversi lavori volti ad indagare le dinamiche, la portata, le cause e le conseguenze dell'aumento di peso legato alla terapia antiretrovirale. L'obiettivo della nostra breve revisione è quello di dare una panoramica dei dati più recenti riguardanti l'aumento di peso nelle PCH presentati al CROI 2021.

Abstract

With the advent of combined antiretroviral therapy (cART), the number of people living with HIV (PLWH) who are virosoppressed (HIV-RNA<50 copies/mL) has increased reaching 90% in high income countries, transforming HIV infection into a chronic disease. The incredible efficacy of the new generations of drugs must necessarily be associated with substantial tolerability.

While older antiretroviral were associated with lipoatrophy and lipodystrophy, new antiretroviral drugs, and in particular the regimens containing integrase inhibitors (INSTI), seem to lead to weight gain and abdominal fat accumulation.

This may lead to an increased risk of diabetes mellitus, metabolic syndrome, and cardiovascular disease, a risk already increased in PLWH compared to HIV-negative persons. Several studies have been conducted about INSTI, in particular about dolutegravir, since they seem to be more likely causative of weight gain.

However, there are still many aspects to be clarified, including the pathophysiological mechanisms underlying weight gain, health consequences and predictors of weight gain.

Several studies investigating the trajectories, magnitude, causes and consequences of weight gain related to cART were presented at CROI 2021. With this brief review we want to give an overview of latest data presented during the focus on fat and weight gain at CROI 2021.

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Thanks to the introduction of combined antiretroviral regimens (cART), HIV infection has become a chronic condition, in which, at present, therapy should be continued lifelong. In this context, cART efficacy and its long-time tolerability become crucial for proposing a durable treatment and guarantee good adherence (1,2). cART regimens currently recommended by national and international guidelines are all characterized by high efficacy, safety, and long-term benefits in people living with HIV (PLWH) (3,4).

The past generation of cART has been associated with many adverse effects on body composition, including lipodystrophy and lipoatrophy syndrome. The new generation of cART, especially integrase inhibitors (INSTI), has been associated with a significant weight gain and an increase of visceral and subcutaneous fat accumulation.

Weight gain is not only an aesthetic issue but could potentially increase the risk of developing diabetes, metabolic syndrome, and cardiovascular disease in PLWH. However, the long term effects of weight gain on health are still to be investigated (5,6).

Different studies have been conducted on weight gain in PLWH receiving INSTI showing a higher weight increase in those receiving dolutegravir when compared to other INSTI and non-INSTI-based regimens. However, the pathophysiologic mechanisms of this difference are still unknown (7,8).

Furthermore, cART regimens containing tenofovir alafenamide (TAF) have been demonstrated to have higher weight gain risk as compared to those containing tenofovir disoproxil fumarate (TDF) (9–11). In the ADVANCE trial, conducted in South Africa, three regimens were compared (TAF/emtricitabine (FTC)/dolutegravir (DTG) vs. TDF/FTC/DTG vs. TDF/FTC/efavirenz (EFV)). The results showed that weight gain during the study was significantly higher in the TAF/FTC/DTG group. Furthermore, females were more affected by weight gain than males. Few data are available in the literature regarding the correlation between weight gain and gender in PLWH, especially in Caucasian females (12). Available data about risk factors related to weight gain in PLWH are summarised in ***Table 1***.

As part of CROI 2021, several studies on weight gain and PLWH were presented. Most of the studies focused on the association between INSTI based regimens and weight gain.

Taken together these data confirm that INSTI can lead to a more pronounced and faster weight gain when compared to other types of cART.

Apparently, there are no differences in how each INSTI can affect body weight (13), including new long-acting (LA) regimen based on cabotegravir (CAB)-rilpivirine (RPV) which showed no significant difference when compared with oral therapy(14).

Furthermore, data about weight gain trajectories were also presented. Palella and colleagues presented data from a retrospective study assessing the impact of TAF and INSTIs on timing, persistence, and magnitude of body weight gain. They examined records from 736 patients who have been virally suppressed for one year on a non-INSTI based ART. Patients have been switched to a non-INSTI or INSTI regimen.

Four groups were taken into consideration: INSTI with TAF, INSTI without TAF, non-INSTI with TAF and non-INSTI without TAF. Regarding patients treated with regimens including INSTI and TAF, the results showed that weight gain was greater and mostly attributable to INSTI in the first eight months, whereas 73% of weight gain was attributable to TAF during the following eight months. The monthly rate of weight gain was faster in patients treated with INSTI, while TAF was associated with a more gradual increase in body mass index (BMI).

No statistically significant difference in the risk of weight gain was highlighted regarding different INSTI when multivariable analysis considering demographic and baseline features of patients was performed (15).

Naive	Virologically suppressed
Female Sex	Female sex
African ethnicity	African and Latino ethnicity
Injection drug users	Having more than 60 years
Low BMI (<18.5)	Low CD4 (<200 cells/mm^3)
Low CD4 (<200 cells/mm^3)	Combination of TAF+INSTI (especially with DTG>RAL>EVG/c)
High HIV-RNA load (>100,000 copies/mL)	
Opportunistic infections	
INSTI regimes compared to PI and NNRTI Among INSTI: DTG=BIC>RAL>EVG/c Among NRTI: TAF	

Table 1. Weight gain risk factors in naive patients and in virologically suppressed experienced patients switching ART.

BIC: *bictegravir;* ***BMI:*** *body mass index;* ***DTG:*** *dolutegravir;* ***EVG/c****: elvitegravir/cobicistat;* ***INSTI****: integrase strand transferase inhibitor;* ***NNRTI****: non-nucleoside reverse transcriptase inhibitors;* ***NRTI****: nucleoside reverse transcriptase inhibitors;* ***PI****: protease inhibitors;* ***RAL****: raltegravir;* ***TAF****: tenefovir alafenamide;* ***TDF****: tenofovir disoproxil fumarate*

Regarding predictors of weight gain, data on different ethnic groups were reported. Relation between black people and risk of weight gain and obesity is particularly significant and needs to be further explored (16).
Preliminary data on Latinos and Haitians were also presented. In this ethnic group, weight gain seems to be faster than in Caucasian people (17). Other possible predictors have been identified, such as pre-ART BMI (18), sex (19), age, CD4+ cell count and viral load. Their role needs to be assessed with further investigations.
In-vitro studies modelling effects of INSTI on adipocytes showed a decrease in leptin and adiponectin secretion, suggesting that this could be one of the mechanisms leading to weight gain (20).
Metabolomic changes in women receiving INSTI have been investigated by Lahriri et al. who identified possible energetical pathways involved in weight changes related to INSTI use (21). Furthermore, effects on white and brown adipose tissue were also investigated. The model presented by Jung et al. suggests that metabolomic changes can act through oestrogen receptors to inhibit mitochondrial proteins in brown adipose tissue. This could partially explain the higher odds of weight gain in women receiving INSTI (22).
Pourcher et al. conducted an interesting study on people living without HIV and PLWH receiving or not INSTI regimens, that performed bariatric surgery. The authors evaluated inflammatory patterns in subcutaneous adipose tissue (SCAT), visceral tissue, and liver parenchyma. Patients receiving INSTI did not show inflammation in SCAT, while some patients from the other two groups did, suggesting that INSTIs may have an anti-inflammatory effect. In addition, patients receiving INSTI showed less steatosis and a milder liver profile (23). In conclusion, during the CROI 2021 new evidence confirmed the role of INSTI in weight gain, especially when associated with TAF. The latest updates are an important tool for physicians and PLWH, since predictors of weight gain have been highlighted. However, further studies need to be conducted to better clarify the mechanisms at the basis of weight composition changes. Contributing factors, such as "return to health" phenomenon, low pre-cART BMI, gender, ethnicity, diet and physical activity must be considered. ■

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