Weight gain stopping/switch rules for antiretroviral clinical trials

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Obesity develops in a substantial number of people initiating and maintaining modern antiretroviral therapy. The comorbidities associated with obesity make significant weight gain and metabolic changes a major consideration in clinical trials studying different regimens' potency and safety. It is as yet unclear what role individual antiretrovirals or classes play in weight gain but the issue is a complex one for clinical trial design, especially when deciding when ''too much'' weight has been gained, in a context where we do not yet know if switching to alternative regimens will slow, halt or reverse weight gain or metabolic changes. In addition, clinician and trial participant opinion on acceptable weight gain may differ. We offer preliminary guidance for discussion for future antiretroviral clinical trial design.

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Introduction

Progressive, significant weight gain leading to obesity has emerged as a major and complex side effect associated with newer antiretroviral treatment (ART) regimens. Future clinical trials of ART will need to be mindful of the extent and pattern of weight gain and associated metabolic changes. As with all considerations of trial outcomes and safety endpoints, standardized guidelines will protect participant safety and autonomy, while preserving trial integrity and ensuring data are valid, comparable across-studies, and clinically meaningful.

To develop such guidelines, there is a need for accepted trial stopping rules, for both naive and switch studies. This is complicated. Weight gain in ART trial participants can be expected, with a 'return to health' as viral control occurs. In addition, weight gain, which is part of the normal ageing process (along with changes in fat : muscle ratios), is not always associated with metabolic consequences, and is not consistently or immediately associated with clear clinical harm. Moreover, a clear definition of a clinically deleterious weight threshold is still debated, and there appears to be substantial geographic, sex and race differences in terms of outcomes [1–6]. For many conditions, including infectious

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diseases, cancer and older age, a lower weight than traditionally labelled 'normal' is clearly associated with greater mortality [2]. There are also widely heterogeneous cultural and ethnic views on what is a 'normal' weight [7]. Many patients welcome weight gain at treatment initiation and indicate that they would prefer to remain on these drugs, raising issues around autonomy, nonmaleficence and beneficence.

BMI is commonly used to assess obesity, despite a poor correlation with actual fat mass. Although it is easy to measure, and is stratified into standardized categories, BMI is limited by variable correlations with clinical outcomes. There is considerable debate around the implications of weight gain in the general public, with several studies drawing into question BMI-based categories labels including 'overweight' (BMI of 25–29.9 kg/m^2) and even 'obese' (30–34.9 kg/m^2) [2]. One large South African study even suggesting all-cause mortality was lower in these two categories, when measured against a traditionally defined 'normal' BMI (18.5–24.9 kg/m^2), this in a context where over half of adult South Africans are categorized as 'overweight' or 'obese' [7,8]. This builds on a substantial amount of work in richer countries, suggesting (controversially) that these categories overestimate risk, and may underestimate risk among people in the 'normal' BMI category [2,3].

Notwithstanding the variable data on the effects of modest weight gain on health and wellbeing in people with HIV, being severely overweight is clearly a health issue. Severe obesity is associated with a wide array of adverse outcomes, including diabetes, hypertension, cardiovascular disease, obstructive sleep apnoea, cancers, osteoarthritis and higher mortality with coronavirus disease 2019 (COVID-19) [3,4]. These impacts extend to babies of obese pregnant women; modelling studies using recently published weight gain on newer ART regimens suggests that initial concerns around dolutegravir-linked teratogenicity will be far outweighed by the impact of maternal obesity on infant outcomes [9].

Researchers are faced with the complexity of trying to allocate attributable risk for individual antiretroviral drugs, when different classes (and even individual drugs within classes) appear to be associated with varying impacts on weight. Individual drugs may even slow weight gain or cause a loss of weight.

In short, significant weight gain has complex ethical, clinical and practical implications that affect study design, oversight and monitoring, and participant preferences during ART development. Regulators will need to issue guidance that balances these issues and guides the pharmaceutical industry and independent researchers on future studies. Similar quandaries face public sector programmes and guideline committees faced with recommending choices to healthcare workers and patients in routine care.

When did weight gain become a dominant issue in HIV therapy?

Lipoatrophy and lipohypertophy were complex major toxicity features with the thymidine analogues, protease inhibitors and efavirenz, and the mechanisms never adequately explained during the period they were in widespread use [10]. Sex and race differences were noted in the incidence and manifestations with these side effects [11].

The first major report of weight gain with newer ART regimens was signalled in mid-2017, with participants discontinuing treatment in observational cohorts after a switch from efavirenz to integrase inhibitor (INSTI)-based therapy. Subsequently, multiple reviews flagged weight gain as a feature of newer treatment regimens, which seemed particularly severe not only with the newer integrase inhibitors, and with tenofovir alafenamide (TAF) but also observed with rilpivirine and protease inhibitors [12,13]. Initial registration studies for TAF and both dolutegravir and bictegravir suggested impressive durability, potency and side effect profiles, whereas weight gain was not reported. Instead, these findings were noted later in independent observational cohorts and both independent and industry meta-analyses.

Early INSTI registration studies recruited largely male and white participants with preserved CD4$^+$ counts, who on average were borderline overweight; early nonregistration studies also largely recruited white men. Subsequent studies suggested that women, black participants (men and women), and those with more advanced HIV disease (lower CD4$^+$ counts, higher viral loads) were most at risk for weight gain and obesity [14]. These groups were largely left out of efficacy studies, which may partially explain why such an overt side effect was missed.

With older drugs, like tenofovir disoproxil fumarate (TDF) and efavirenz, higher drug exposure may be related to less weight gain because of gastrointestinal symptoms, lipoatrophy or other unclear mechanisms; however, when the older drug is switched to a modern antiretroviral, weight gain is often significant [12]. In people who are efavirenz extensive metabolizers because of CYP2B6 polymorphisms, weight gain is similar to those on dolutegravir; those who had intermediate or slow metabolism had more blunted gain [15]. The precise mechanisms for these weight changes remains unclear.

Current advice for those experiencing weight gain is limited to the usual diet and lifestyle measures. There is no clear evidence that switching drug classes will mitigate weight gain, or whether timing of switches, either early or

late in the trajectory, matters. Finally, ART drug choices are very limited in many resource-constrained countries, where HIV is most prevalent [16].

The ADVANCE and NAMSAL studies and weight gain

The ADVANCE trial was designed to evaluate the efficacy and safety of TAF compared with TDF, and dolutegravir compared with efavirenz, with the study currently extended to 192 weeks. The study was described in detail elsewhere but the rationale for the study design was that TAF offered lower renal and bone toxicity over TDF, and dolutegravir greater tolerability, a better metabolic profile, and resistance benefits over efavirenz, allowing for the WHO to make firm recommendations regarding the use of these two drugs, aligning to the standard of care in higher income countries [16–19]. The study was designed prior to the recognition of weight gain as a side effect associated with TAF or dolutegravir use.

Weight gain was significant but particularly severe in the dolutegravir-containing arms, and even worse in the arm containing TAF (7.1 kg in the TAF/emtricitabine+dolutegravir group; 4.3 kg in the TDF/emtricitabine+dolutegravir group, and 2.3 kg in the TDF/emtricitabine/efavirenz group)). Weight distribution was fairly even between trunk and limbs, when measured by dual-energy X-ray absorptiometry (DXA). Metabolic and blood pressure changes associated with this obesity thus far have been small, and of uncertain clinical significance, but 96-week changes are regarded as very short term for these types of changes, especially as patients were young and would have ample beta-cell pancreatic reserve.

Weight gain was slightly greater in the NAMSAL study from Cameroon [although participants had more advanced disease (lower mean $CD4^+$ counts and higher viral loads), and weighed less at antiretroviral initiation than the ADVANCE participants], which evaluated dolutegravir against a 400 mg dose of efavirenz, both in combination with TDF and lamivudine, and also showed greater emergence of obesity among women. Weight gain was greater in the TDF/lamivudine+dolutegravir group, with a median weight gain of 5 kg at week 96, as compared with a median weight gain of 3 kg for those on low-dose efavirenz [20].

This consultation drew the following from the above evidence:

(1) New generation integrase inhibitors confer neuropsychiatric tolerability, resistance benefits, and persistence over efavirenz. TDF/lamivudine (or emtricitabine) and dolutegravir remains the WHO-recommended first-line standard of care in South Africa since late 2019 [19]. Early reports of metabolic changes on switching to TDF/3TC/dolutegravir from African programmes are concerning [21,22]. The South African Department of Health has been notified of the weight data, and continues to recommend the WHO regimen but is cautiously monitoring this through a pharmacovigilance programme.
(2) TAF provides laboratory-measured renal function and bone mineral density benefits over TDF but the clinical consequences of this remain uncertain; the impact of TAF on the dolutegravir-containing arm rate of weight gain was significant. TAF is only recommended by the WHO for nephrotoxicity and osteoporosis patients currently, with important questions remaining about safety in pregnancy and drug interactions with rifampicin [19].

ADVANCE and NAMSAL continues to monitor and treat metabolic parameters as well as relevant clinical (including cardiovascular events and malignancies) parameters, such as blood pressure, and advocate lifestyle and dietary changes in all participants gaining weight, as both studies have been extended to 192 weeks.

Input from participants, clinicians, and community advisors

Most ADVANCE participants initially expressed satisfaction with weight gain, irrespective of regimen, even with the evolution of morbid obesity ($BMI > 40\,kg/cm^2$). Perceptions that dolutegravir was better than efavirenz was evident throughout the course of the study because of community education and media reports on anticipated benefits, with many participants on the efavirenz arm wanting to switch to dolutegravir arms. When investigators discussed switching participants to efavirenz from dolutegravir (initially as it was felt that dolutegravir was the cause of the obesity), many participants expressed dismay; some even said they would go to the state clinics if switched to efavirenz, where dolutegravir is standard of care and where they were very likely to receive that combination. No similar reaction was seen with TAF, probably because of far less community education and media attention on the drug. However, patients, predominantly women, have begun to express dissatisfaction with the magnitude of the weight gain, despite emphasis on lifestyle changes.

In the NAMSAL trial, no patient switched off dolutegravir because of weight gain concerns. ADVANCE clinicians on the study expressed discomfort with passively observing participants experiencing severe weight gain, while acknowledging the lack of data regarding switching from either dolutegravir or TAF on the weight gain trajectory.

Participant and community perception of clinical obesity are complex [7]. Being underweight has traditionally attracted stigma around perceptions regarding HIV and TB status. Being overweight has connotations in some

societies pertaining to wealth and status. These perceptions are not just within our region; anecdotal evidence from many treating HIV clinicians in the United States and Europe suggest a subset of patients are pleased with their weight gain. Finally, perceptions are constantly altering, as body perceptions of health change, especially in urban areas. In a large community consultation of community treatment activists from across Africa and held in Rwanda, participants expressed concern about the lack of options for switching in low-income and middle-income settings, if they began gaining unacceptable levels of weight [23].

In South Africa, there have been many informal reactions by healthcare workers to the weight gain signal, as the South African Department of Health has rolled out dolutegravir-containing regimens to largely replace efavirenz. Approaches to mitigating weight gain are as per national general obesity guidelines, which is of major concern in South Africa public health circles, where the majority of women are overweight or obese [7]. Many clinicians have expressed concern with the extent of the reported weight gain on ADVANCE, noting that dietary and physical activity modification are usually ineffectual, especially if patients do not view weight gain as unwelcome, and access to many of the foods found in dietary recommendations impractical or expensive. Some clinicians have even indicated that they would over-ride patient autonomy, and prescribe efavirenz in place of dolutegravir for obese patients (alternatives to dolutegravir and efavirenz, such as rilpivirine or doravirine are not available for routine state patient programmes).

ADVANCE proposal

For ADVANCE, we recommend the following for continuing study participation, balancing autonomy and harms after consultation with participants, community groups and clinicians (these recommendations are under considerations by the regulator and ethics committee:

(1) The TAF arm continues to give us valuable data on safety and pregnancy as one of the few randomized studies using this combination in these communities, especially if TAF finds a place within WHO guidelines for ART treatment or in preexposure prophylaxis.
(2) A renew consent process for all participants on the dolutegravir arms with a new BMI greater than 30 kg/ cm^2 and at least one new metabolic complication (diabetes, hypertension or lipid elevation – all using local reference guidelines) or anyone with an existing BMI greater than 35, whereby they are offered a voluntary switch to the efavirenz arm. Participants will be informed about the implications of continued weight gain, that efavirenz is implicated in diabetes and lipid abnormalities but associated with weight gain at lower rates than dolutegravir and that the switch may be associated with significant neuropsychiatric side effects, especially in those who experience weight gain mitigation; they will be counselled that switch may not impact on weight gain trajectory or metabolic parameters.
(3) A mandatory switch of TAF to the TDF/dolutegravir arm for all participants with a new BMI greater than 30 and a rise of greater than 10% (to prevent switching patients from 28.5 to 30 kg), or a rise of 10% or more if BMI greater than 30 pre-ART. Again, we clarify we do not know for certain if this switch would temper future weight gain.
(4) All switches will only occur if a recent viral load is undetectable within 3 months, and a follow-up viral load will be done to ensure sustained suppression after 3 months. All participants in the study would continue on the study if providing consent even if switched; this will allow us to gain observational data in this post hoc period of the trials on whether switch strategies impact on weight gain.

A more generic approach for future antiretroviral studies

In the future, we recommend the following guidance for weight and metabolic monitoring for clinical trials of ART:

(1) We do not believe excluding people with a BMI greater than 30 kg/ cm^2 from studies is in the interests of public health or ethical principles pertaining to justice. We need generalizable data that equitably includes individuals from both sexes and all races, especially in the context of a worldwide obesity epidemic.
(2) A new BMI greater than 30 kg/cm^2 once enrolled on a clinical trial, or a gain of more than 10% of body weight if initiated with a BMI greater than 30 kg/cm^2, is a useful simple threshold to begin evaluating therapeutic options and switches, even though this threshold is not yet well correlated with actual body fat or clinical outcomes.
(3) The state of knowledge regarding antiretroviral switches on weight gain trajectories is likely to rapidly accumulate in the next few years, and switch strategies built into protocols at inception; uncertainty regarding this impact on the trajectory or on metabolic changes, should be clearly communicated to research participants when discussing changing regimens.
(4) In addition, the uncertainty around the consequences of weight gain, especially where there is not a clear impact on metabolic parameters, should similarly be communicated.
(5) As lifestyle modification is so intricately linked to behaviour change, studies should seek the guidance of dieticians, behavioural scientists, and even mental health professionals, when designing lifestyle intervention advice packages.
(6) Studies on newer antiretrovirals should include standardized evaluations of weight, height (and, ideally, waist and hip measurements), and associated metabolic changes (at a minimum glucose/HbA1c and lipids); it may be prudent

to add DXA where budgets allow (in the entire cohort or in a sample), as we learn about the pattern of weight gain and associated metabolic changes. Studies may also want to further evaluate and document any dietary or lifestyle interventions during the course of the study.

(7) Where there is equipoise or where benefits and harms are complex (as in the case of dolutegravir versus efavirenz), we believe participant autonomy and choice, after careful explanation of implications of these choices, should guide decision-making, and considering the impact on randomization.

(8) In cases where there is clear harm over benefit – as in the weight gain is associated with clear metabolic consequences or severe obesity developing – stopping rules related to BMI thresholds may override autonomy.

(9) If a participant is switched, they should be retained under observation and the data presented in the publication wherever possible, to allow comprehensive assessment of study participation and the impacts of switching on metabolic and HIV-related outcomes.

(10) Classifying weight gain as a Serious Adverse Event requires future consideration, as this may facilitate more rapid intervention.

(11) Mechanistic understanding of the reasons for weight gain are needed, and both basic science and qualitative complimentary studies, including endocrinologic pathways, genetic and pharmacogenetic studies, and experiential understanding of participant perspectives around weight gain should inform part study planning. Finding a simple biomarker associated with weight gain and inflammation could also greatly assist treatment programmes.

(12) Researchers should take care regarding categoric statements on obesity and weight gain; there is substantial scientific uncertainty regarding the actual clinical consequences within different BMI categories, and notions of 'healthy weight' have been exploited by the fitness, diet, health, and other industries to suit commercial interests [24].

In conclusion, we believe the above recommendations are a starting point for a discussion on stopping/switching rules. A BMI threshold of 30 kg/cm^2 or a gain of more than 10% of body weight if initiated with a BMI greater than 30 kg/cm^2, seems a reasonable starting point, although studies showing that mortality may actually be lower even beyond this; using this threshold to initiate interventions to prevent or delay a progressive rise above 35 kg/cm^2 would seem sensible. We note that BMI is an imperfect and contested measure of weight and obesity; however, in the context of weight changes, we posit that it is a usable, simple marker to guide decision-making. The Food and Drug Administration and other regulators use BMI for evaluating weight loss drug studies, although no such guidance currently exists around weight gain [25]. A standardized way to collect weight data needs to be developed. Alternative measures, such as DXA, anthropometric measurements, ultrasound and MRI scanning may be used but add complexity, do not have widespread consensus regarding classifications, add expense, and probably provide little benefit over BMI to switch decisions to participants in a highly monitored cohort. However, the field would benefit from consensus on which variables, and the mechanisms of measuring these, should be routine in different studies beyond BMI.

In addition to weight and BMI, studies should monitor for consequences of obesity – blood pressure, glucose and lipid monitoring as a minimum. Lifestyle changes and dietary interventions may need to be considered as part of antiretroviral initiation, not just for people developing obesity, as many participants became overweight or obese in ADVANCE and NAMSAL with time. Pharmacovigilance programmes should be including weight and associated complications as a routine part of monitoring.

Where there is clinical equipoise, and where benefits and harms are complex to tease out, as in the debate around switching dolutegravir to efavirenz, we feel participant autonomy based on a clear explanation of the risks and unknowns around switches should be respected, and discussions carefully documented. An informed written consent process could be considered.

Where there is clear harm outweighing the benefit, as occurred here on TAF with those who gained weight, we feel switches should be mandated.

In clinical practice, we do not feel guidance would greatly differ from above, although in resource-constrained settings, the laboratory parameters listed above could be far more limited, and imaging is unlikely to be part of routine care. Practically, especially in less resourced areas, switch options are likely to be severely restricted, and again, careful explanation is merited with patients. Moreover, as most HIV programs in the sub-Saharan African region continue to use a public-health and guideline-based approach, treatment programs require a strong evidence base. It will depend on clinical trials to thoughtfully and rigorously monitor metabolic complications, include reasonable treatment options that balance harm with benefit, and report the medium-term and long-term effects of these strategies for guidelines to ensure they are providing maximum benefit to the populations they represent. Broader consensus on rules for programmatic settings is urgently required.

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