Clinical consequences of weight gain during treatment for HIV infection

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Purpose of review
The introduction of dolutegravir, an oral integrase inhibitor, within public health HIV programs has been a success, with excellent sustained viral load suppression, persistence, and safety. Initial concerns around integrase-inhibitors being implicated in safety concerns around immune reconstitution inflammatory syndromes (IRIS), neural tube defects, and weight gain, have been largely laid to rest, but new concerns about cardiovascular risk have arisen, including a link between hypertension and this antiretroviral class.

Recent findings
We review the pertinent studies here, and while we find both observational and randomized controlled study associations in some but not all studies, these are often confounded by associated weight gain and aging. In addition, definitions of hypertension, as well as measurement within the studies (such as cuff size), were not consistent within studies.

Summary
Careful analysis will be needed, as with the weight-gain signal, before assigning causation, especially as plausible physiological mechanisms for this rise in blood pressure are unclear.

Keywords
dolutegravir, efavirenz, hypertension, tenofovir

INTRODUCTION

The safety profile of dolutegravir has so far been excellent. Compared with efavirenz, dolutegravir shows lower risks of neuropsychiatric adverse events, metabolic disturbance, liver enzyme elevations, and rash. Expanded analyses have shown no increased risks of neural tube defects in the infants of pregnant women. The combination of tenofovir disoproxil fumarate (TDF), with lamivudine or emtricitabine and dolutegravir is the most highly recommended global first-line treatment for HIV infection [1]. Costs of treatment have fallen to $55 per person-year in LMICs; over 19 million people are estimated to be taking dolutegravir-based treatment [2].

DOLUTEGRAVIR, TENOFOVIR ALAFENAMIDE, AND WEIGHT GAIN: A CONFUSION OF ASSOCIATION AND CAUSATION

Weight gain during first-line treatment is higher for people taking dolutegravir versus efavirenz. However, this appears to be because efavirenz leads to attenuation of weight gain, if given to people who metabolize efavirenz slowly [3]. In addition, weight gain tends to be greater for people who take tenofovir alafenamide (TAF) versus TDF. However, in people without HIV taking TDF as PrEP, there have been significantly more reports of weight loss using TDF versus placebo, suggesting an independent effect from TDF [4]. Weight gain tends to be higher for women and people of black race [5,6]. However, there is considerable genetic diversity within Southern Africa. One study in Uganda showed no significant weight gain after the switch from efavirenz to dolutegravir, possibly a function of genetic diversity, but also perhaps a function of food availability and social circumstances [7].

These high levels of weight gain tend to be more common for people taking first-line dolutegravir

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KEY POINTS

- The current safety and efficacy data for dolutegravir support widespread treatment of HIV infection.
- There is ongoing evaluation of the risk of clinical obesity and weight gain, and associated clinical consequences.
- The current evidence is not showing consistent trends. Some studies are suggesting elevated risks of hypertension and other cardiovascular outcomes for dolutegravir, while other studies are showing no differences in risk from other antiretrovirals.
- More clinical trials need to be re-evaluated and published before a comprehensive assessment can be made.

with TAF [5] and also those with baseline $CD4^+$ cell counts below 200 cells/μl, and those with elevated viral loads [8]. Predictive studies using cardiovascular risk equations suggest that these gains in weight could increase the risk of myocardial infarction and Type II diabetes over 10 years [9].

Anecdotally, and understandably, this weight gain is causing concern for both clinicians and patients, as many transition from efavirenz and TDF-containing regimens, and have sudden weight gain. While moving from TAF back to TDF arguably has minimal major consequences, any move from dolutegravir to efavirenz for reasons of effecting weight loss should be strongly discouraged, as slow metabolizers of efavirenz are prone to all the toxic consequences of the drug, and those who are normal metabolizers have the same weight trajectory as patients taking dolutegravir [3].

CONCERNS ABOUT CARDIOVASCULAR RISK AND INTEGRASE INHIBITORS: CONFLICTING RESULTS

Large observational studies have investigated whether there is a higher risk of myocardial infarction and diabetes. The RESPOND study evaluated 29 340 people, of whom 14 000 (48%) received an integrase inhibitor. After 6 years of follow up, the incidence of cardiovascular disease events was 4.2/1000 for those with no exposure to INSTIs, which rose to 8.5/1000 in the first 6 months of INSTI exposure, and then fell to 4.3/1000 in longer term follow up [10], but that selection bias might explain these results [11▪].

Contradicting these results (and using participants that were included in the RESPOND cohort), the Swiss HIV cohort evaluated 5362 participants, of whom 1834 (34.3%) started integrase inhibitors [12▪▪]. There were 116 cardiovascular events recorded, with no significant differences by use of integrase inhibitors, regardless of follow-up time.

In a retrospective analysis of the IBM MarketScan database of 14 000 people in the USA, people taking integrase inhibitors had a significantly higher risk of congestive heart failure or myocardial infarction or lipid disorders. However, there were no associations between INSTI use and the risk of coronary artery disease, stroke/transient ischemic attack, hypertension, Type 2 diabetes or metabolic syndrome [13▪▪].

Evaluating the risk of rare cardiovascular endpoints within randomized clinical trials should provide more reliable results. However, the available randomized trials comparing integrase inhibitors with other treatment classes are limited in sample size and follow up time [14]. Cardiovascular endpoints have not been recorded in a standardized procedure, which would allow a meaningful interpretation in meta-analysis. In addition, cardiovascular events are complex, with variable local diagnostic abilities, and may take many years for risk factors to accumulate to declare themselves clinically, making short-term clinical trials poor venues for study.

HYPERTENSION – RESULTS FROM RANDOMIZED TRIALS

Hypertension is a major, modifiable but undertreated risk factor for cardiovascular disease, with substantial epidemiological overlap with HIV in much of the world, making any association of considerable clinical concern.

Table 1 summarizes the hypertension results from randomized trials of first-line treatment.

In the NAMSAL trial, 624 people with HIV (PWH) in Cameroon were randomized to 192 weeks of first-line TDF/lamivudine/dolutegravir or TDF/lamivudine/efavirenz (400 mg dosage). In the ADVANCE trial, 1053 PWH in South Africa were randomized to 192 weeks of first-line TAF/emtricitabine/dolutegravir, TDF/emtricitabine/dolutegravir, or TDF/emtricitabine/efavirenz (conventional 600 mg dosage). In both trials, blood pressure was measured at every study visit. Grade 1 hypertension was defined as SBP/DBP more than 140/90 mmHg. In ADVANCE, all participants developing Grade 1 hypertension were given antihypertensives, according to South African treatment guidelines. In NAMSAL, less than 1% of participants were given antihypertensives, as funding was not available [15].

In NAMSAL (Fig. 1, Table 2), SBP rose by 10 mmHg by Week 192 in the TDF/lamivudine/dolutegravir arm, versus 3.5 mmHg on TDF/lamivudine/efavirenz ($P < 0.001$). By Week 192, 18% of participants developed Grade 1 hypertension on

Table 1. Hypertension outcomes from randomized controlled trials of first-line treatment

Clinical trial	Treatment arms	Results
ADVANCE [15] first line, $n=1053$	TAF/FTC/DTG TDF/FTC/DTG TDF/FTC/EFV	Week 192: higher risk of treatment-emergent hypertension
NAMSAL [15] first line, $n=613$	TDF/FTC/DTG TDF/FTC/EFV	Week 192: higher risk of treatment-emergent hypertension
SPRING-1 [16] $n=205$	2NRTI+DTG 2NRTI+EFV	Week 96: no significant difference in SBP
SINGLE [16] $n=833$	ABC/3TC+DTG TDF/FTC+EFV	Week 96: no significant difference in SBP
FLAMINGO [17] $N=484$	2NRTI+DTG 2NRTI+DRV/r	Week 96: higher risk of treatment emergent hypertension for DTG versus DRV/r
SPRING-2 [16] $n=822$	2NRTI+DTG 2NRTI+RAL	Week 96: no significant difference in SBP
Gilead 1489 [18] $n=629$	TAF/FTC/BIC ABC/3TC/DTG	Week 144: DTG and BIC similar
Gilead 1490 [18] $n=645$	TAF/FTC/BIC TAF/FTC/DTG	Week 144: DTG and BIC similar

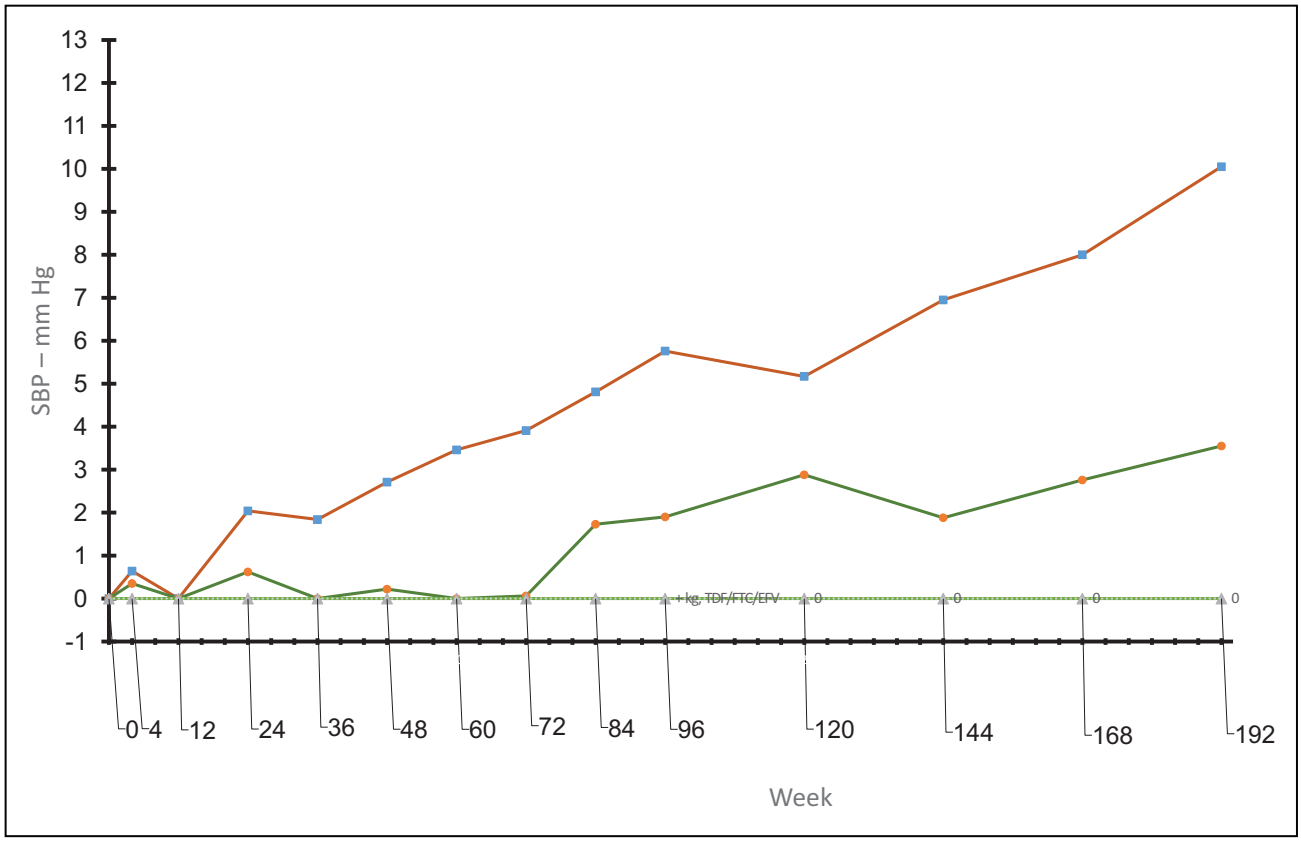

FIGURE 1. NAMSAL trial. Mean change in SBP over time.

Table 2. NAMSAL trial, percentage of participants with graded hypertension at Week 192

Grade, SBP/DBP	Definition	TDF/3TC/DTG	TDF/3TC/EFV	*P*
Grade 1	>140/90	46 (18%)	29 (13%)	<0.01
Grade 2	>160/100	20 (8%)	14 (6%)	0.02
Grade 3	>180/110	19 (7%)	4 (2%)	<0.01

TDF/lamivudine/dolutegravir, versus 13% on TDF/lamivudine/efavirenz ($P = 0.002$) (Table 3). Less than 1% of participants were treated with antihypertensive drugs. In multivariate analysis, Grade 1 hypertension was significantly correlated with use of dolutegravir, age, sex, and BMI ($P < 0.01$ for each comparison).

In ADVANCE (Fig. 2, Table 3), 6% of patients were already being treated for hypertension at baseline, rising to 20% by Week 192. Treatment-emergent Grade 1 hypertension was diagnosed for 42/315 (13%) participants on TAF/emtricitabine/dolutegravir, 33/316 (10%) on TDF/emtricitabine/dolutegravir, and 25/314 (8%) taking TDF/emtricitabine/efavirenz (Table 4). The risk of Grade 1 hypertension was significantly higher for TAF/emtricitabine/dolutegravir versus TDF/emtricitabine/efavirenz ($P = 0.04$). However, 95% of participants with treatment-emergent hypertension were given antihypertensives. By Week 192, there was no significant difference in mean SBP or Grade 1 hypertension between the arms. In multivariate analyses of these trials, the difference in risk of hypertension between treatment arms was no longer significant when adjusted for changes in body weight over time [15].

A pooled analysis of 96-week data of randomized trials evaluated hypertension for dolutegravir versus other treatments. This analysis included results from studies comparing dolutegravir with efavirenz (SINGLE and SPRING-1) and darunavir/ritonavir (FLAMINGO). These studies enrolled participants mainly from Europe and North America, where access to antihypertensives is widely available. During 96 weeks of evaluation, there were no significant differences in the mean change of either SBP or DBP between dolutegravir and the control arms for SINGLE and SPRING-1 [16]. However, in a follow up analysis looking at treatment-emergent Grade 1 hypertension, there was a significantly higher risk for dolutegravir versus darunavir/ritonavir in the FLAMINGO trial [17].

Results from first-line head-to-head studies comparing different integrase inhibitors suggest similar rises in blood pressure within the class. These similar effects have been seen in the SPRING-2 study, comparing dolutegravir with raltegravir [16], and in the Gilead 1489 and 1490 studies, comparing dolutegravir with bictegravir [18].

As summarized in Table 4, several studies of second-line treatment have also suggested higher risks of hypertension for dolutegravir. The 2SD study, conducted in Kenya, recruited people with undetectable HIV RNA while taking protease inhibitor based treatment. They were randomized to remain on boosted protease inhibitors (typically either lopinavir/ritonavir or atazanavir/ritonavir) or to switch to DTG. After 48 weeks of randomized treatment, the percentage reporting hypertension as a Grade 1–4 clinical adverse event was 11.6% for DTG versus 5.6% for protease inhibitor/r ($P = 0.018$). This difference was seen despite a small difference in weight gain between the arms (+1.5 kg for dolutegravir, +1.0 kg for lopinavir/ ritonavir) [19▪].

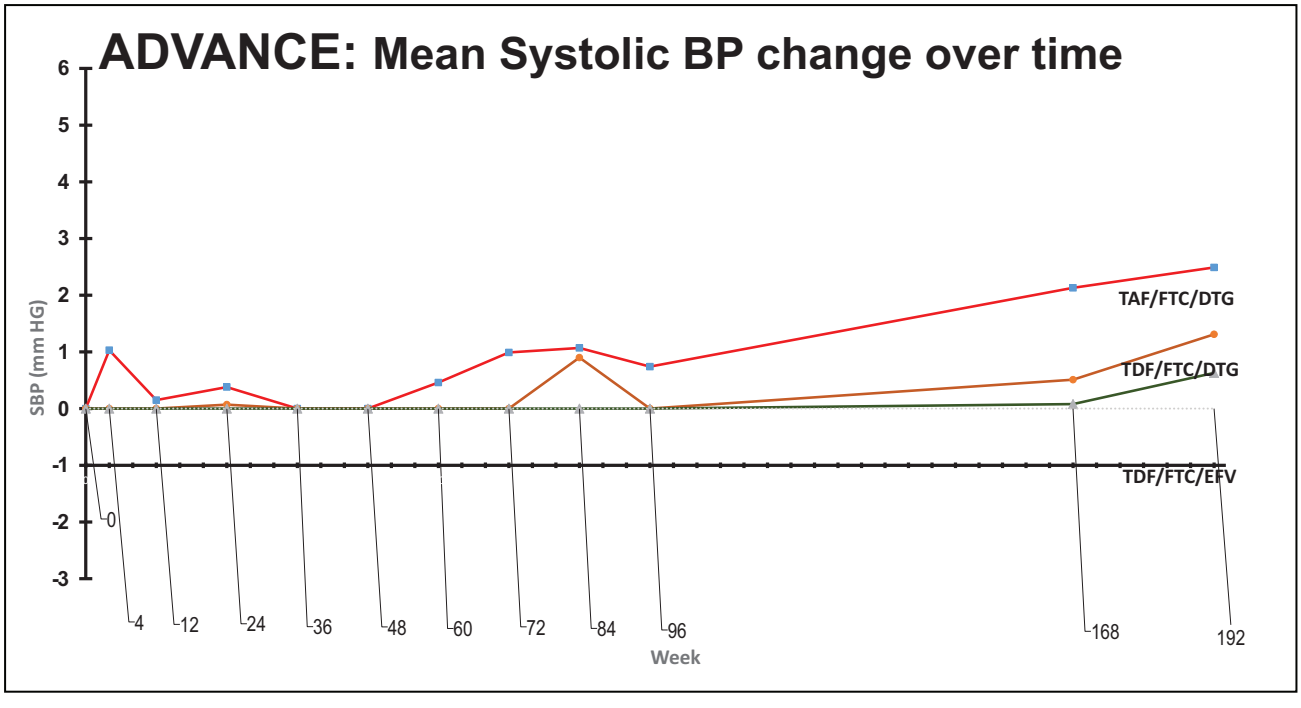

FIGURE 2. ADVANCE trial. Mean change in SBP over time.

Table 3. DAIDS graded hypertension (baseline to week 192)

	TAF/FTC+DTG *n/N* (%)	TDF/FTC+DTG *n/N* (%)	TDF/FTC/EFV *n/N* (%)
Hypertension at baseline	36/351 (10%)	35/351 (10%)	41/351 (12%)
New hypertension	42/315 (13%)	33/316 (11%)	25/310 (8%)
New hypertension treated	42/44 (100%)	30/33 (91%)	22/25 (88%)

Treatment-emergent Grade 1 hypertension significantly higher for TAF/FTC/DTG versus TDF/FTC/EFV ($P=0.038$).

The D2EFT trial enrolled people who had prior virological failure on NNRTI-based treatment. They were randomized to receive either TDF/emtricitabine/dolutegravir, optimized nucleoside reverse transcriptase inhibitors (NRTIs) and darunavir/ritonavir, or the combination of dolutegravir and darunavir/ritonavir. After 48 weeks of randomized treatment, mean rises in SBP were significantly higher in the TDF/emtricitabine/dolutegravir and darunavir/ritonavir+ dolutegravir arms, compared with the 2NRTI+darunavir/ritonavir arm [20].

The NEAT-022 trial, conducted mainly in Europe, recruited people with undetectable HIV RNA while taking boosted protease inhibitor based treatment. They were then randomized either to continue the protease inhibitor based treatment or to switch to dolutegravir for 48 weeks. There was no significant difference between the arms in mean changes of either SBP or DBP at week 48 [21▪].

MISSING REGISTRATION CLINICAL TRIALS DATA

Three companies are responsible for all the clinically available integrase inhibitors on the market. Several key randomized trials do not have results on hypertension available for review (Table 5). ViiV has only collected clinical adverse event reports associated with hypertension during most of their clinical trials. These adverse event reports only account for 15% of the high blood pressure results, according to the meta-analysis presented by ViiV where they analyzed their trials where both clinical adverse events and all blood pressure reports were available. The new randomized trials of cabotegravir need to be evaluated to determine whether hypertension is also an issue with this new integrase inhibitor.

RESULTS FROM OBSERVATIONAL STUDIES

Table 6 shows the currently available results from nonrandomized cohort studies.

In the TSEPAMO cohort [22], conducted in Botswana, the risk of hypertension was compared between three groups of women: 2079 taking dolutegravir-containing regimens from conception, 3735 taking efavirenz-containing regimens from conception and 10 598 women without HIV. The risks of any hypertension or gestational hypertension were significantly higher for women taking dolutegravir versus those taking efavirenz. However, the overall risks of hypertension for women with HIV taking dolutegravir were significantly lower than in women without HIV. In multivariate analyses, changes in body weight did not fully explain the differences in hypertension seen between treatment groups.

In the RESPOND cohort [23], risks of hypertension were evaluated over time for 9704 PWH who did not have hypertension at the baseline visit. Of the 9704 participants, 2977 (30%) developed hypertension over 39 993 person-years of follow up. Hypertension was more common with the use of

Table 4. Hypertension results from second-line studies

Clinical trial	Treatment arms	Results
NEAT 022 [21▪] Switch, $n=415$	2NRTI+DTG 2NRTI+PI/r	Week 48: no significant difference in SBP
2SD [19▪] Switch, $n=795$	2NRTI+PI/r 2NRTI+PI/r	Week 48: Grade 1 HTN 11.6 versus 5.8%, $P=0.018$
D2EFT [20] second line	TDF/FTC/DTG 2NRTI+DRV/r DRV/r+DTG	Week 48: Mean SBP higher for DRV/r+DTG

Table 5. Key randomized clinical trials of DTG with results not available

Clinical trial	Treatment arms	Results
First-line treatment		
VESTED	TAF/FTC/DTG TDF/FTC/DTG TDF/FTC/EFV	Analysis completed
ARIA $n=495$	ABC/3TC/DTG TDF/FTC+ATV/r	Results not available >10% reporting threshold
GEMINI $n=1433$	TDF/FTC/DTG 3TC+DTG	Results not available >5% reporting threshold
ODYSSEY-A $n=311$	2NRTI+DTG 2NRTI + EFV	Results not available
Second-line treatment		
NADIA	TDF versus ZDV DTG versus DRV/r (factorial)	Analysis completed
VISEND	TAF/FTC/DTG TDF/FTC/DTG ZDV/3TC/PI/r	Analysis completed
SWORD-1 and 2 Switch, $n=1024$	DTG+RIL Current ART	Results not available >5% reporting threshold
STRIIVING Switch, $n=553$	ABC/3TC/DTG Current ART	Results not available >5% reporting threshold
Gilead 1844 Switch, $n=563$	ABC/3TC/DTG TAF/FTC/BIC	results not available >5% reporting threshold
SALSA Switch, $n=493$	DTG/3TC Current ART	Results not available >5% reporting threshold
TANGO Switch, $n=741$	DTG/3TC Current ART (TAF)	Results not available >5% reporting threshold
SAILING second line, $n=715$	2NRTI + DTG 2NRTI + RAL	Results not available >5% reporting threshold
DAWNING $n=627$	2NRTI+DTG 2NRTI+LPV/r	Results not available (>5% reporting threshold)
ODYSSEY-B second line, $n=396$	2NRTI+DTG 2NRTI + PI/r	Results not available

INSTIs and TAF. These effects remained significant after adjusting for changes in BMI over time. INSTIs and TAF were also associated with higher risks of dyslipidemia [24].

In the REPRIEVE cohort, the baseline data from 4500 participants was used to evaluate risks of hypertension by treatment history. People who had taken dolutegravir were significantly more likely to have hypertension than those not taking INSTIs [(RR = 1.4, 95% confidence interval (95% CI) = 1.2–1.7]. However, those taking either raltegravir or elvitegravir/cobicistat at baseline did not show increased risks of hypertension compared to non-INSTI users [25].

In the Johannesburg cohort [26▪▪], 794 people with undetectable HIV RNA levels switching from efavirenz to dolutegravir were matched to 794 controls who remained on efavirenz-based treatment. After 48 weeks of follow up, Grade 1 hypertension was observed for 25% of those switching to dolutegravir versus 11% those remaining on efavirenz ($P<0.001$), but with a higher change in mean weight for the people who switched to dolutegravir (+1.8 kg).

In the Women's Interagency HIV study [27], 1118 participants were followed for a median of 2 years. Compared to the non-INSTI group, the INSTI group experienced greater increases in HbA1C (+0.05 versus 0.06 mg/dl, $P=0.03$), SBP (3.84 versus 0.94 mmHg, $P=0.019$), and DBP (+1.62 versus 0.14 mmHg, $P=0.01$) [27].

In a cross-sectional study conducted in Zambia, the prevalence of hypertension was 18.4% (64/384 participants). Participants on dolutegravir -based treatment were two times more likely to be hypertensive compared to those taking efavirenz or nevirapine ($P=0.01$) [28].

Hypertensive disorders of pregnancy were evaluated in a USA study. Among 265 women living with HIV, INSTI containing regimens were

Table 6. Hypertension outcomes from observational studies

Study	Design	Result
TSEPAMO	$n=5824$	Higher risk of HTN for DTG versus EFV, but risks lower than HIV- controls
RESPOND	$n=4606$	Higher risk of HTN from use of INSTI and TAF
REPRIEVE	$n=4500$	Higher risk of HTN with DTG
Johannesburg	$n=1588$	Higher risk of HTN for DTG versus EFV (switch cohort)
WIHS cohort	$n=1118$	Higher increases in SBP and DBP with INSTI
Zambia	$n=348$	Higher risks of HTN with DTG
US study	$n=345$	Higher risks of HTN in pregnancy with INSTI
Spain	$n=219$	Higher increases in SBP and DBP with INSTI

associated with an increased risk of any hypertensive disorders of pregnancy: 25% among INSTI users, versus 10% for those taking protease inhibitors. There were also higher risks of gestational hypertension for INSTI users (20%) versus those taking protease inhibitors (8%). Overall, the risk of hypertensive disorders was similar among pregnant women living with HIV on ART, compared with a control group of pregnant women without HIV [29].

ISSUES WITH INTERPRETATION OF HYPERTENSION IN CLINICAL TRIALS

There are several issues with the current analyses of hypertension in HIV clinical trials and observational studies:

(1) Dolutegravir continues to show sustained benefits over efavirenz, both in terms of virological suppression, resistance, and safety.
(2) The results on hypertension from clinical trials so far have been inconsistent, with no clear explanation.
(3) It is important that the correct cuff size is used to measure blood pressure for people with high BMI [30]. Those with BMI more than 35 kg/m^2 can have artificially high readings if normal sized cuffs are used, as is the case in most clinics, including clinical trials sites. The results from the ADVANCE and NAMSAL trials were repeated excluding data from people with BMI more than 35 kg/m^2, and the overall results were not affected.
(4) When interpreting the results from non-randomized, observational studies, we cannot exclude the potential for bias and unmeasured confounding. Ten years ago, observational studies showed a higher risk of IRIS for people taking integrase inhibitors. However, then the randomized REALITY trial showed no additional risks.
(5) There is high background prevalence of hypertension in the population with high HIV prevalence, particularly in sub-Saharan Africa.
(6) It is not clear whether rises in blood pressure during first-line treatment are the result of rises in weight, as part of a 'return to health' effect. In the TSEPAMO study, women taking dolutegravir had a higher risk of hypertension than those taking efavirenz. However, the risk of hypertension on dolutegravir was still lower than in matched HIV negative controls [22].
(7) Blood pressure rises with age, so any monitored cohort will see a natural rise.
(8) Even if there is a difference in the risk of hypertension between dolutegravir and efavirenz, or between TAF and TDF-based treatment [31], this may not be sufficient reason to change treatment. Hypertension can be monitored and treated using cheap generic drugs. Given the high background prevalence of hypertension and other NCDs in the general population, the priority should be to integrate the treatment of NCDs within HIV access programs, if possible.

RISKS OF DIABETES FROM INTEGRASE INHIBITOR USE

A systematic review and meta-analysis of 13 randomized controlled trials and six observational cohort studies has shown no significant increase in the risk of Type 2 diabetes for people taking integrase inhibitors [32]. The most commonly reported endpoint was fasting hyperglycemia of at least Grade 2, or HbA1C above 6.5%. In the subset of studies from sub-Saharan Africa, there was a threefold increase in the risk of Type 2 diabetes. Since the publication of this meta-analysis, results from two large observational studies have suggested that integrase inhibitors are associated with higher risks of Type 2 diabetes. The U.S. IBM MarketScan database [33] included results from 42 382 patients, and showed a 31% increase in the risk of diabetes for people taking integrase inhibitors. The RESPOND cohort [34] showed a 48% increase in the risk of Type 2 diabetes for people using integrase inhibitors. More integrated research is needed to investigate the reasons for different outcomes between these studies.

CONCLUSION

It will be important to continue the evaluation of hypertension and other metabolic outcomes for a wide range of clinical trials. The independent effects of NRTI backbones on hypertension could be evaluated by analysis of older trials comparing TDF with TAF, for example.

Analysis of studies of people without HIV infection (e.g. during PrEP or for the treatment of HBV) could allow an independent evaluation of drug effects, without the confounding effects of 'return to health'.

Clinical trials need to be evaluated using consistent methods. For example:

(1) Consistent grading of hypertension using the standardized cut-off levels for the DAIDS grading system (for example SBP/DBP >140/90 mmHg for Grade 1). Mean changes in blood

pressure by treatment arm should also be reported.
(2) exclusion of people with hypertension at baseline, who could be analyzed separately.
(3) data on new use of antihypertensive drugs included in the analysis.
(4) results analyzed using mean changes from baseline, as well as the percentage with Grade 1, 2, and 3 hypertension.
(5) information on the prevalence of hypertension in the general population, for the countries included in each clinical trial.
(6) outcomes from programmatic studies, where available.

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Conflicts of interest

Andrew Hill declares no conflicts of interest. Francois Venter has received honoraria for advisory boards with ViiV and Merck, not connected to this project.

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