

23 August 2019: no 10

*Further IAS 2019 reports: ART strategies, weight gain, PrEP*

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## h-tb

### HIV TREATMENT BULLETIN

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## EDITORIAL

### This bank holiday edition of HTB continues with further reports from the IAS 2019 conference.

These include several important studies on ART strategies.

Importantly, we highlight that reduced dosing (4 vs 7 days a week) are NOT equivalent options due to the risk of serious drug resistance with some combinations.

We also report the unexpected association of weight gain with dolutegravir in the randomised South African ADVANCE study.

Other reports on integrase inhibitors include use of dolutegravir in younger children in Odessey study and a review of several studies reporting high efficacy of switching to bictegravir/F/TAF, with analyses for drug resistance.

We also include on the PK analysis from the DISCOVER study that reports on potential advantages of F/TAF for PrEP in people with low adherence.

### SUPPLEMENTS

#### U=U resources for UK clinics: free posters, postcards and factsheets

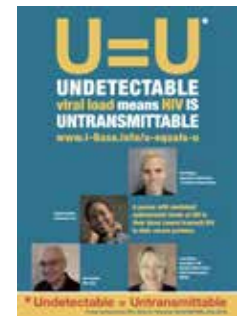
Please continue to order these free resources.



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For further information please contact Roy Trelvelon at i-Base: [roy.trelvelon@i-base.org.uk](mailto:roy.trelvelon@i-base.org.uk)



### i-Base 2019 appeal

This year we are continuing a funding appeal to help i-Base continue to provide free publications and services.

Your help has been inspiring – and we hope this support will continue during 2019. If 1000 people support us with £5 a month we will be on course to meet our funding shortfall. All help is appreciated.

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## CONFERENCE REPORTS

### 10th IAS Conference on HIV Science (IAS 2019)

21-24 July 2019

#### Introduction

Simon Collins, HIV i-Base

The 10th IAS Conference on HIV Science (IAS 2019) in Mexico City was held from 21 – 24 July 2019.

The programme is posted online, with abstracts and PowerPoint slides available for many of the presentations.

<http://www.ias2019.org>

Reports in the last issues of HTB focussed on:

- New antiretroviral drugs.
- ART strategies with new and existing drugs.
- An important (and optimistic) update on neural tube defects with dolutegravir, with a comprehensive review of the latest data.
- Updates to WHO treatment guidelines

HTB reports in this issue include:

- For days on, three days off is NOT as effective as daily ART: French study results need to be interpreted with caution
- Switching to bictegravir/F/TAF in virally suppressed participants including analyses by baseline drug resistance
- Dolutegravir-based first-line non-inferior to efavirenz-based ART but associated with substantial weight gain: results from the ADVANCE study
- Dolutegravir for younger children: results from the ODYSSEY trial
- PK advantages of TAF/FTC over TDF/FTC for HIV PrEP might compensate for low adherence: sub-analysis of DISCOVER study



#### IAS 2019: ANTIRETROVIRALS

### For days on, three days off is NOT as effective as daily ART: French study results need to be interpreted with caution

Simon Collins, HIV i-Base

Early results from a late-breaker study at IAS 2019 reported that reduced-dose ART had similar outcomes as a switch strategy compared to people who continued taking ART every day. However, this led to multidrug resistance in people with treatment failure and is therefore difficult to recommend, certainly not for people on rilpivirine or raltegravir. [1]

As background, studies that support less than daily dosing – FOTO in adults and BREATHER in children and young adults – used efavirenz/emtricitabine/TDF as these drugs all have long half-lives. Both these studies reported that this specific combination does allow dosing five days a week, with weekends off. [2, 3] A Spanish group also used this combination to drop down to only three doses a week but only included 30 people. [4]

In contrast, several French groups, have used reduced dosing irrespective of individual drugs. These have generally been small observational studies that are not powered to show either safety or efficacy. [5, 6]

The new results at IAS 2019 are controversial because a randomised study is seen as providing a high level of evidence. However, the detailed results showed there was a real risk of viral load rebound. And depending on the individual drugs in the combination, the rebound led to multidrug resistance.

Results were presented by Roland Landsman from Université Paris Diderot as a late-breaker oral abstract.

This study randomised 647 participants on stable ART (viral load < 50 copies/mL for >12 months) – and with no history of drug resistance – to either switch to 4 consecutive days per week (4/7) or to remain on daily 7-day ART (7/7). However, only 636 participants who started the study were included in the modified intent-to-treat analysis (318 in each arm) and only 623 were included in the per protocol analysis (n=313 vs 310).

Baseline characteristics were balanced between arms and included median age 49 years (IQR: 41 to 55); 85% were male; 78% were European, 14% African. Viral load was <50 copies/mL for a median of 5.8 years (IQR: 3.3 to 9.6) and median CD4 count was 689 cells/mm<sup>3</sup>(IQR: 533 to 884). CD4 nadir was 298 cells/mm<sup>3</sup> (IQR: 195 to 419).

Just under half the group were using either NNRTI- or integrase-based ART, with 6% using a boosted PI. The breakdown by dual NRTIs included TDF/FTC (56%), TAF/FTC (16%) and abacavir/3TC (27%).



The study enrolled very quickly, within four months – from September 2017 to January 2018 – and the last person reached week-48 follow-up by April 2019. The primary endpoint was viral suppression at week-48 with follow-up extending for another year (during which participants in the 7/7 arm switched to 4/4 dosing. Substudies will look at pharmacokinetic (PK) drug levels, markers of inflammation and immune activation, total DNA and viral load in semen and a quality of life survey.

At week 48, viral load remained undetectable in 95.6% in the 4/7 group vs 97.2% in the 7/7 group (adj. diff. –1.6%; 95% CI: –4.5% to 1.3%). This met the definition for non-inferiority using the predefined margin of 5% cut-off. It also met non-inferiority for treatment failure (1.9% vs 1.3%) using the FDA upper margin of 4%.

Viral failure was reported by 6 (1.9%) vs 4 (1.3%) participants in the 4/7 and 7/7 groups respectively.

In subgroup analyses, there were no differences by CD4 nadir, CD4:CD8 ratio, duration <50 copies/mL or previous viral failure. However, although not reported as statistically significant, numerically there were more viral failures in the 4/7 group in participants on INSTI-based ART (n=3 vs n=1), similar failure on NNRTIs (n=3 in each arm) and no viral failures in people using PI-based ART.

The two deaths in the 4/7 arm were due to cardiac arrest and lung cancer.

Summary details for the 10 cases of viral failure included that drug resistance was reported in 3/6 vs 1/4, respectively. All three of the participants in the 4/7 arm with drug resistance failed with two-class resistance (2 x rilpivirine + 3TC/FTC and 1 with raltegravir + 3TC/FTC). The single case of drug resistance in the 7/7 arm was to rilpivirine only.

Most of these cases of viral failure were detected very early, when viral load was confirmed at low levels in 3/4: at 105, 129, 230 and 75,000 copies/mL. Switching to three-drug ART brought viral load to <50 copies/mL.

Viral blips did not occur more frequently in the reduced dosing arm.

There were no differences in adverse events between the two arms, including for liver enzymes and lipid results, except for eGFR which significantly improved in the 4/7 arm: +5.5 mL/min (95% CI: –1.2 to +13.6 vs +1.3 mL/min (95% CI: –6.1 to +7.5),  $p < 0.001$ .

Although the study concluded that this strategy could save money in high income settings, the presenter also wrongly suggested that this would enable more people to access ART in low income settings.

Firstly, results from a high income country with easy access to sensitive viral load and resistance testing cannot be transferred to countries where there are higher rates of background drug resistance, significantly fewer treatment options less access to sensitive monitoring (viral load tests commonly have a cut-off at 1000 copies/mL and are only available once a year).

Secondly, drug costs only make up a much smaller percentage of overall management costs in low- compared to high-income countries. Any short-term cost savings on drug could easily be lost on additional complications relating to management of HIV drug resistance.

## C O M M E N T

**The multidrug drug resistance results in participants on NNRTI or INSTI based ART whose viral load rebounded is more important than the non-inferiority findings.**

**In an earlier study these researchers reported that reduced dosing leads to suboptimal drug levels for some participants. The development of drug resistance in the context of sub-optimal drug levels is only a factor of luck and time and with longer follow up more people are likely to see their treatment fail.**

**The PK properties of rilpivirine make it especially unsuitable for anything other than daily dosing and this is probably also the case with integrase inhibitors.**

**Similarly, the low failure rate that allowed non-inferiority is likely to be explained by use of NRTIs with a long intracellular half-life, providing dual therapy cover for most of the three days off-ART. Drug resistance on dual therapy is just a matter of time and luck.**

**Also, France is a high-income country that has easy access to sensitive viral load tests and resistance tests for people in who this strategy fails.**

**Monitoring is likely to be more frequent in a clinical study than in routine care, with treatment failure detected very early. Less frequent monitoring (often 6-12 monthly) might lead to extensive drug resistance in a real world setting. This risks both the development of more complex drug resistance and HIV transmission.**

**This study does however provide good evidence that modern ART is easily able to cover odd missed doses, even if this is once or twice and for most weeks.**

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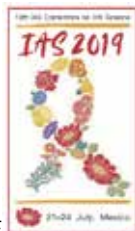
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## High efficacy from switching to bicitgravir/F/TAF in virally suppressed participants – including analyses by baseline drug resistance

### Simon Collins, HIV i-Base

Several studies at IAS 2019 presented data on switching to bicitgravir/FTC/TAF (B/F/TAF).

Paul Sax from Brigham and Women's Hospital, Boston, presented results from a randomised double-blind phase 3 study (4030) switching people with undetectable viral load on stable dolutegravir (DTG)-based ART (plus either FTC/TDF or TFC/TAF).



The study randomised 565 participants to B/F/TAF (n=284) or DTG+F/TAF (n=281). Although history of integrase resistance was an exclusion criteria, documented drug resistance to NRTI, NNRTI and protease inhibitors was allowed.

Approximate baseline characteristics included median age 50 years (IQR: 20 to 79), 85% men. 70% white, 22% Black/African and 22% Hispanic/Latino. Median CD4 count was about 640 cells/mm<sup>3</sup> (IQR: 460 to 885).

At week-48, viral load was <50 copies/mL by snapshot analysis in 93% vs 91% in the B/F/TAF vs DTG+F/TAF arms respectively. The results for primary endpoint of viral failure (>50 copies/mL) was <1% vs 1% (n=1 vs 3), meeting criteria for non-inferiority (diff. -0.7%, 95% CI: -2.8 to 1.0) using 4% margin. Sensitivity analyses using <20 copies/mL cut-off reported undetectable viral load in 91% vs 86% overall and 64% vs 60% for target not detected (B/F/TAF vs DTG + F/TAF).

Adverse events were similar between arms, including leading to drug continuation (n=6 in each arm (2.1%) and including grade 3.4 laboratory abnormalities. No significant differences in lipids were reported between arms with similar use of lipid lowering drugs at baseline through to week-96.

There were also no differences in rates of viral suppression between arms in the 24% participants with previous NRTI resistance: K65R or >2 thymidine analogue mutations (TAMS) (94% vs 93%) or other NRTI (87% vs 87%). No participants in either group with previous NRTI resistance developed detectable viral load over 48 weeks and there were no newly emergent integrase-related mutations. Further results on drug resistance in this study were included in a separate poster. [2]

Another two posters provided similar reports of viral suppression with baseline drug resistance.

Andreatta et al looked at drug resistance in 510 participants in the control arms of two switch studies who rolled over into the open label extension (OLE) to receive B/F/TAF for a median of 60 weeks (IQR: 48 to 72). [3]

Cumulative baseline genotypic data were available for NRTI in 73% (373/510) and integrase in 49% (248/510), with primary mutations in 11% (41/373) and 3.6% (9/248), for NRTI and integrase respectively. DNA genotyping detected previously undocumented M184V/I in 5.4% (20/373), and TAMs were observed in 8.0% (30/373).

However, 99% (503/510) of participants had viral load < 50 copies/mL at last visit, including 95% (19/20) with archived M184V/I, 100% (30/30) with TAMs, and 100% (9/9) with integrase resistance. No new resistance was detected during the OLE in the five participants who met criteria for resistance testing.

Acosta et al presented a second poster looked at low level baseline resistance using deep sequencing in 1270 treatment-naive participants in a further two studies. [4]

Additional primary resistance mutations not found by population sequencing were detected in 3.7%, 3.7%, 4.2% and 5.8% for NRTI, integrase, NNRTI and PI-associated mutations, respectively. Overall, participants with low-frequency resistance mutations had viral load < 50 copies/mL at week 96 at similar rates similar to the overall study.

In women, Cissy Kityo from the Joint Clinical Research Centre in Kampala presented results 96-week phase 3 results from 470 women on stable selected ART regimens who were randomised (1:1) to either switch to once-daily B/F/TAF or remain on their current ART. At week-48, participants in the control arm were switched to B/FTAF until week-96. [5]

This was an open-label study with sites in the Dominican Republic, Russian Federation, Thailand, Uganda, and the US. Baseline regimens at entry was elvitegravir/cobicistat/F/TAF (54%), E/C/F/TDF (43%) or atazanavir + ritonavir + F/TDF (5%).

Baseline characteristics at randomisation included median age 40 years (range: 21 to 64), median CD4 count 701 cells/mm<sup>3</sup> (IQR: 539 to 895) and baseline eGFR was 100 (IQR: 83 to 117). Ethnicity included black/African (37%), white (28%), Asian (22%) and Hispanic/Latino (15%). Only six women had viral load that was detectable >50 copies/mL.

Although B/F/TAF looks to have produced high rates of viral suppression these results were presented as as Missing = Excluded analysis (M=E), rather than by more strict Missing=Failure (M=F) analyses. Unsurprisingly, >98% virologic outcomes were reported for both timepoints in both arms (as on-treatment analyses tend to do). For example, 234 women were originally randomised to B/F/TAF but at week-96 the denominator for the 99.5% success reported is based on only 208 women (207 of whom had viral load <50 copies/mL).

Side effects were reported for almost the whole study (462/470) but only for the time on B/F/TAF (ie without the week-48 results from the control arm).

Overall, most side effects were grade 1/2. Grade 3/4 adverse events (AEs) were reported by 7% (n=31/462) of women using B/F/TAF, with 6% (n=27/462) judged related to study drugs. Serious AEs were reported by 5% (24/462) but only led to one study discontinuation.

No new cases of drug resistance were reported to B/F/TAF in either group through to week-96. One person on E/C/F/TAF in the control arm with viral rebound and the M184V mutation resuppressed after switching to B/F/TAF.

Small improvements were linked switching from TDF-containing combinations to TAF and although no lipid changes were reported as significant, again, this was only reported for B/F/TAF exposure and not for the control arm at week 48.

Finally, Jean-Michel Molina from Saint Louis Hospital, Paris, presented 24-week results in 86 HIV positive participants older than 65 years who switched to open-label B/F/TAF from E/C/F/TAF or a TDF-based regimens. Follow-up in this study will continue out to week 96.

Baseline characteristics included: mean age 70 years (range 65-80), 13% were female, and 99% were white. Median weight was 78 kg (range: 49 to 110) and eGFR was 76 mL/min (range: 40 to 130). Baseline ART was E/C/F/TAF for 91% (78/86) of participants.

At week-24, 98% participants remained <50 copies/mL, again using Missing=Excluded (M=E) analysis - as 2 participants had missing data and 2 discontinued (with last viral load <5- copies/mL).

Tolerability was good with no grade 3/4 events and no change in weight, although median eGFR declined by -4.5 mL/min at week 12 and was then stable out to week 24.

## COMMENT

**These studies support high efficacy of B/F/TAF as a switch option in different populations including continued viral suppression with baseline mutations.**

**It is unclear why results are being presented as observed rather than full intent-to-treat analyses, when at least both should be presented.**

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## Dolutegravir-based first-line non-inferior to efavirenz-based ART but associated with substantial weight gain: results from the ADVANCE study

Polly Clayden, HIV i-Base

**Dolutegravir (DTG)-based ART was non-inferior to efavirenz (EFV)-based treatment in a South African study comparing three first-line regimens. [1, 2] Participants receiving DTG experienced significant rises in weight and this was more pronounced among those also receiving tenofovir alafenamide (TAF). [3]**



Week 48 safety and efficacy data from the ADVANCE study were presented at IAS 2019, alongside a simultaneous publication in the New England Journal of Medicine (NEJM). A pooled analysis with the NAMSAL trial, looking at body weight, was also shown at the conference.

### ADVANCE

ADVANCE is a 96-week, open-label, randomised trial conducted by the newly-hatched Ezintsha – a sub-syndicate of the Wits Reproductive Health and HIV Institute (Wits RHI) – and colleagues.

The study is currently underway in Johannesburg and compares TAF/emtricitabine (FTC)/DTG, tenofovir disoproxil fumarate (TDF)/FTC/DTG and TDF/FTC/EFV.

Participants aged 12 years and above, with no previous ART for more than 30 days, creatinine clearance greater than 60 mL/min (80 mL/min if less than 19 years) and viral load greater than 500 copies/mL were included. Pregnancy and tuberculosis (TB) were exclusion criteria.

Participants did not have baseline genotyping, in accordance with South African treatment guidelines. Background NNRTI resistance in South Africa is estimated to be 5–15%.

The primary endpoint was week 48 viral load less than 50 copies/mL, discontinuation or missing data (Intent-to-treat population, non-inferiority margin -10%, significance level  $p=0.017$ , adjusted for multiple comparisons).

Professor Francois Venter from Ezintsha presented the findings on behalf of the ADVANCE investigators.

A total of 1053 participants (351 per arm) were randomised between February 2017 and May 2018: 99% black, 60% women, mean age at baseline 32 years and CD4 336 cells/mm<sup>3</sup>. Approximately 20% had viral load over 100,000 copies/mL. Baseline median Body Mass Index (BMI) was 24.1 kg/m<sup>2</sup>.

The percentage of participants with viral load <50 copies/mL at week 48 were: 83.8% for TAF/FTC/DTG, 84.9% for TDF/FTC/DTG and 78.6% for TDF/FTC/EFV. In the on-treatment analysis the respective percentages were: 96% for TAF/FTC/DTG, 94% for TDF/FTC/DTG and 95% for TDF/FTC/EFV.

Professor Venter noted that social issues played a greater role in participants achieving virological suppression than regimen, particularly age and employment. Rates for young and unemployed people were about 60% compared to older employed people who achieved almost 100% suppression.

The study confirmed non-inferiority for both DTG arms versus the EFV arm.

The majority of participants with viral load >50 copies/mL re-suppressed after adherence counselling. Only 2/18 in the TAF/FTC/DTG arm, 3/19 for TDF/FTC/DTG and 7/16 for TDF/FTC/EFV did not re-suppress. There was no DTG-emergent resistance.

Adverse events and laboratory abnormalities were similar between treatment arms with the notable exception of weight gain.

### Weight gain

In the 96 week NAMSAL trial, 613 treatment naive participants in Cameroun were randomised to TDF/3TC/DTG or TDF/3TC/EFV 400 mg. Body weight was measured at baseline and week 48.

In ADVANCE, body weight was measured at baseline and every 12 weeks. DEXA scans evaluated limb and trunk fat at baseline, weeks 48 and 96.

Dr Michelle Moorhouse from Ezintsha showed data from a pooled analysis of the two trials: changes in body weight and BMI were compared between arms. Changes in trunk fat were also compared between arms in ADVANCE.

Participants in NAMSAL were 66% women, with a median age of 37 years. At baseline, median BMI was 23 kg/m<sup>2</sup>, CD4 approximately 280 cells/mm<sup>2</sup>, 67% had viral load above 100,000 copies/mL and 30% above 500,000 copies/mL.

This analysis revealed that in NAMSAL mean weight rose by a mean of 5 kg (BMI 1.7 kg/m<sup>2</sup>) for TDF/3TC/DTG vs 3 kg (BMI 1.2 kg/m<sup>2</sup>) for TDF/3TC/EFV (both  $p < 0.001$ ). Treatment-emergent clinical obesity (BMI >30 kg/m<sup>2</sup>) was seen in 12% of participants on TDF/3TC/DTG vs 5% on TDF/3TC/EFV ( $p < 0.01$ ).

At week 48, 44% of women in the TDF/3TC/DTG arm had 10% or more change from baseline weight vs 34% in the TDF/3TC/EFV arm ( $p < 0.05$ ). For men, the difference was non-significant and the percentage with 10% or more change was about 20%.

The difference in treatment-emergent obesity between arms was greater in men than women. In the TDF/3TC/DTG vs TDF/3TC/EFV respectively: 14% vs 2% ( $p < 0.01$ ) compared with 12% vs 7% (NS).

ADVANCE bodyweight changes overall are shown in Table 1. There were highly significant differences in weight change between arms ( $p < 0.001$ ). Treatment-emergent clinical obesity was higher in the TAF/FTC/DTG arm than other two arms ( $p < 0.01$ ).

**Table 1: ADVANCE changes in body weight**

ART regimen	TAF/FTC/DTG	TDF/FTC/DTG	TDF/FTC/EFV
Mean change in weight			
Week 48	+6 kg	+3 kg	+1 kg
Week 96	+8 kg	+5 kg	+2 kg
Treatment-emergent overweight			
Week 48	23%	14%	9%
Week 96	25%	13%	11%
Treatment-emergent obese			
Week 48	14%	7%	6%
Week 96	19%	8%	4%

At the time of analysis, not all participants had reached week 96.

In men, there were greater mean increases in weight in the two DTG arms compared to the EFV arm and these were higher in the TAF arm than the TDF-containing arms. Up to week 48, changes in weight were progressive in the DTG arms, after which the rate of increase appeared to plateau.

DEXA scanning, found changes in trunk and limb fat to be higher with DTG-based treatment: +5.4 kg, +4.3 kg and + 0.5 kg, in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively at 96 weeks.

Dr Moorehouse noted that most of the weight gain in the DTG arms is fat gain (both trunk and limb). In the EFV arm, although both limb and trunk fat increased at weeks 48 and 96, at week 96 there was a loss of lean trunk mass.

As weight changes were slightly lower with DEXA, she also explained that participants were weighed at each visit and, although the intention was to perform DEXAs on everyone, this was not always possible as the very obese might have been too big for the scanner so the DXA data might underestimate mean weight change compared to the main analysis.

Similarly, for women, there were greater percentage weight changes in the two DTG arms compared to the EFV one. And this was more pronounced in the TAF than the TDF-containing arm. Women receiving TAF/FTC/DTG experienced an average 16% weight increase over 96 weeks.

But, unlike men, the women's percentage weight change increases were progressive and linear in the DTG arms up to week 96 and do not appear to be reaching a plateau.

DEXA scans, also found changes in trunk and limb fat to be higher with DTG-based treatment: +9.2 kg, +5.4 kg and +2.8 kg, in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively at 96 weeks.

In multivariate analysis (adjusted for socio-demographics, baseline factors, disease history and adverse events and concomitant medications), TAF/FTC/DTG, baseline CD4 count, baseline viral load, and baseline BMI were predictive of treatment-emergent obesity. Excluding baseline BMI, female sex, South African nationality, and employment were also significant.

TAF/FTC/DTG, baseline CD4 count, baseline viral load, female sex, age, and baseline weight were predictive of a 10% or more increase in body weight.

#### C O M M E N T

**ADVANCE is ongoing, further analyses are underway as all participants reach 96 weeks and the study will continue to monitor people to see what happens in the long-term. Ideally the plan is to continue follow up for at least another two years (week 192). The study team are actively pursuing funding to do this.**

**The huge strength of these data is the inclusion of 60% women (and almost all black African participants) in a low- and middle-income setting. In ADVANCE, there are also DEXA scans, which, as Professor Venter pointed out, were in place to look at bone density in the three treatment arms but turned out to be very useful for the weight changes analysis.**

**Regular HTB readers will have heard this over and over again, but once again, these findings are a rallying cry for greater diversity in clinical trials rather than the typical 80–85% white men (still) seen in registrational trials for new drugs. Having data across populations that are treated is a vast improvement on guessing things will be OK as antiretrovirals are rolled out to millions of people.**

*Polly Clayden is on the scientific committee of ADVANCE and co-author of the NEJM paper.*

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IAS 2019: PAEDIATRIC CARE

## Dolutegravir for younger children: results from the ODYSSEY trial

**Polly Clayden, HIV i-Base**

**Dolutegravir (DTG) dosed according to World Health Organization (WHO) weight bands in children weighing 10 kg to 20 kg, achieved similar concentrations to adults and older children. But pharmacokinetic (PK) profiles showed high variability in the 6 kg to 10 kg weight band group.**



These findings, from a nested PK sub study of the ODYSSEY trial, using the ViiV Healthcare 5 mg dispersible tablet (DT) formulation, were presented at IAS 2019.

ODYSSEY is a phase 3, randomised, non-inferiority trial comparing DTG-based ART to first- and second-line standard of care in children and adolescents.

Data were shown from children weighing 6 kg to < 20 kg. Children weighing 6 kg to <10 kg, 10 kg to <14 kg and 14 kg to < 20 kg received DTG DT at 15 kg (3 tablets), 20 mg (4 tablets) and 25 mg (5 tablets) once-daily dosing, respectively.

DTG DT is approximately 1.6 to 2 times more bioavailable than the adult film coated tablets (FCT).

Target reference values were those achieved in adults receiving DTG 50 mg once-daily and twice-daily with C<sub>trough</sub> being the primary target: 0.83 mg/L (CV 26%) and 2.72 mg/L (CV 70%). The investigators also evaluated individual levels above target EC90 (0.32 mg/L) and/or IC90 (0.06 mg/L).

Sampling was at steady state (at least 7 days) and fasted in children over 10 kg and, where possible, younger children.

Of 41 children enrolled from Zimbabwe, Uganda and South Africa, 34 had evaluable PK curves and were included in the analysis: 11, 10 and 13 in the 6 kg to <10 kg, 10 kg to <14 kg and 14 kg to <20 kg weight bands respectively. The youngest participant was 6 months old and the oldest 2.5 years.

The analysis found that DTG DT in children weighing 10 kg to <14 kg and 14 kg to <20kg, dosed once daily, according to WHO weight bands, achieved similar C<sub>trough</sub> to adults.

But children in the 6 kg to <10 kg weight band had lower geometric mean (GM) C<sub>trough</sub>, more frequent levels below EC90 (4/11) and PK profiles showed high variability.

Results were also similar to those seen in older children and the IMPAACT P1093 study. [2]

#### C O M M E N T

**Further PK data collection is ongoing in children in the 3 kg to <6 kg weight band receiving 5 mg if less than and 10 mg if more than 6 months of age.**



**Both ODYSSEY and IMPAACT P1093 PK data will be included in submissions to FDA and EMA.**

**Generic manufacturers are developing dispersible scored 10 mg DTG tablets to accommodate WHO paediatric weight bands with fewer tablets/formulations.**

*Polly Clayden is on the trial steering committee of ODYSSEY.*

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IAS 2019: PrEP

## PK advantages of TAF/FTC over TDF/FTC for HIV PrEP might compensate for low adherence: sub-analysis of DISCOVER study

**Simon Collins, HIV i-Base**

**A new analysis from the large phase 3 international DISCOVER study showed that the better pharmacokinetic (PK) properties of F/TAF over F/TDF could lead to advantages in some populations, especially if adherence is difficult. [1]**



The results from DISCOVER study was presented earlier this year at CROI, finding non-inferiority for TAF/FTC compared to TDF/FTC. In this study 5,387 gay men and transgender women at high risk of HIV were randomised (1:1) to either daily F/TAF or daily F/TDF with matching placebo. At the primary endpoint (when 50% of participants had reached week 96) there were 22 infections: 7 vs 15 in the F/TAF vs F/TDF arms respectively. This gave an incidence of 0.16 vs 0.34 per 100 patient years of follow up (PYFU) and an incidence rate ratio (IRR) of 0.47 (95%CI: 0.19 to 1.5) numerically showing a 53% advantage for F/TAF meeting criteria for non-inferiority (though importantly this was not statistically significant).

After allowing for people who were found to be HIV positive at baseline (n=1 vs 4), only one participant in each arm became HIV positive with medium or high drug levels suggesting good adherence. However, with suboptimal drug levels, there were fewer new infections with F/TAF (n=5 vs 10). See Table 1.

**Table 1: HIV infections in DISCOVER study**

	F/TAF	F/TDF
Total HIV infections	7	15
Positive at baseline	1	4
Low drug levels	5	10
Infections with adherence	1	1

As there were no reported differences between arms at any time point in HIV risk based on number of partners, newly diagnosed rectal STIs or adherence this led researchers to use a nested case-control study (matched 1:5) to look for pharmacokinetic differences.

Throughout the study, adherence was high in both arms, with less than 80% adherence (in observed analysis) only reported by <4% of participants by self-report and <8% by pill count at all timepoints. This was also supported by TFV-DP levels in dried blood spot (DBS) in the pharmacokinetic sub-study (n=536), again at all timepoints out to week 96. In both cases and controls, low drug levels by DBS at diagnosis was associated with increased risk of HIV acquisition ( $p<0.001$ ).

This was reported as equivalent to taking less than two doses per week with F/FTAF and less than four doses a week with F/TDF.

These differences were supported in the large PK sub study (n=324) that reported 98% vs 68% of participants in the F/TAF vs F/TDF groups had intracellular drug levels above the EC90. Median TFV-DP in PBMCs were also 6.3-fold higher with F/TAF at 404 vs 61 fmol/million cells.

Two other PK advantages were also reported for F/TAF.

Firstly, protective drug levels are achieved more quickly with F/TAF, with median intracellular levels of TFV-DP reaching EC90 in PBMCs within two hours (and within four hours for all participants), compared to needing three daily doses with F/TDF.

Secondly, after reaching steady state levels with daily dosing, F/TAF provided a longer period of cover after stopping PrEP - keeping TFV-DP levels above the EC90 for a median of 16 days compared to a median of 10 days with F/TDF.

Both these properties would be likely to benefit on-demand dosing but it is important to remember that these analyses were based on comparing earlier PK studies for each formulation and were not linked to efficacy results in DISCOVER.

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6. NYC department of health and hygiene. An "on-demand" dosing schedule for PrEP to prevent HIV. 2019 Alert number 15, (28 June 2019). <https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2019/rep-to-prevent-hiv-alert.pdf> (PDF)
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## C O M M E N T

**The plausibility of better pharmacokinetic properties providing more comprehensive PrEP coverage in the context of low adherence is important.**

**However, the DISCOVER study also showed that in the context of good adherence both formulations are highly effective, with only 22 infections during 8756 PYFU, with no differences in efficacy. Even with on-demand dosing F/TDF is so effective that it is recommended in IAS-USA and EACS guidelines for protection for anal sex. [3, 4]**

**Now branded PrEP 2:1:1 in the US, on-demand dosing is also recommended in certain situations by major US health providers in San Francisco and New York, which is significant given FDA only approved daily dosing.**

**For the majority of people to be able to benefit from F/TAF it will need to be priced much closer to F/TDF.**

**This will need much lower pricing in the UK and other countries that now have access to generic F/TDF.**

### References

1. Spinner C et al. DISCOVER study for HIV pre-exposure prophylaxis (PrEP): F/TAF has a more rapid onset and longer sustained duration of HIV protection compared with F/TDF. 10th IAS Conference on HIV Science. Mexico City. 21–24 July 2019. Oral late breaker abstract TUAC0403LB. <http://programme.ias2019.org/Abstract/Abstract/4898>
2. Hare CB et al. The phase 3 DISCOVER study: daily F/TAF or F/TDF for HIV preexposure prophylaxis. 4–7 March 2019, Seattle. Oral abstract 104. <http://www.croiconference.org/sessions/phase-3-discover-study-daily-ftaf-or-ftdf-hiv-preexposure-prophylaxis>
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## ANTIRETROVIRALS

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### Cabotegravir/rilpivirine long-acting injectable HIV drugs submitted to EMA

Simon Collins, HIV i-Base

**On 29 July 2019, ViiV Healthcare issued a press release announcing that the cabotegravir/rilpivirine long acting subcutaneous injection has been submitted to the European Medicine Agency (EMA). It is likely that this will take 12 month. [1]**

The submission is based on results from the phase 3 ATLAS and FLAIR studies. [2]

US submission to the FDA was three months earlier in April 2019, with a priority review expected by end of December 2019. [3]

#### References

1. ViiV press release. ViiV Healthcare submits regulatory application to European Medicines Agency for investigational cabotegravir to be used in combination with rilpivirine as the first monthly injectable treatment for HIV. (29 July 2019). <https://www.viivhealthcare.com/en-gb/media>
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## FUTURE MEETINGS

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### Conference listing 2019

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

#### 4th European Workshop on Healthy Living with HIV

13 – 14 September 2019. Barcelona

[www.virology-education.com](http://www.virology-education.com)

#### International Workshop on HIV Drug Resistance and Treatment Strategies

16 – 18 October 2019

[www.hivresistance2019.co.za](http://www.hivresistance2019.co.za)

#### 21st Intl Workshop on Comorbidities and Adverse Drug Reactions in HIV

5 – 6 November 2019, Basel, Switzerland

<https://www.intmedpress.com>

#### 10th International Workshop on HIV & Aging

10 - 11 October 2019 | New York, NY, USA

[www.virology-education.com](http://www.virology-education.com)

#### 17th European AIDS Conference

6 – 9 November 2019, Basel

[www.eacsociety.org](http://www.eacsociety.org)

#### 3rd European Chemsex Forum

14-16 November 2019, Paris

<https://ihp.hiv>

## PUBLICATIONS & SERVICES FROM i-BASE

### i-Base website

All i-Base publications are available online, including editions of the treatment guides.

<http://www.i-Base.info>

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

<http://www.i-base.info/qa>

### i-Base treatment guides

i-Base produces six booklets that comprehensively cover important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

<http://www.i-base.info/guides>

- Introduction to ART (May 2018)
- HIV & quality of life: side effects & long-term health (Sept 2016)
- Guide to PrEP in the UK (March 2019)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (Jan 2018)
- Guide to HIV, pregnancy & women's health (April 2019)

### Pocket guides

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### U=U resources for UK clinics: free posters, postcards and factsheets

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This project was developed with the Kobler Centre in London.

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Other i-Base resources can still be ordered online as usual.

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For further information please contact Roy Trelvelion at i-Base:

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