**Adult and paediatric optimised ART trial tracker**

i-Base’s Op ART trial tracker follows research

on optimised antiretroviral treatment for low-

and middle-income countries.



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**Adults**

**Dolutegravir**

**Table 1: First-line ongoing**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study/cohort** | **Design** | **Purpose** | **Status** |
| [ADVANCE](https://clinicaltrials.gov/ct2/show/NCT03122262)  WRHI 060  Wits RHI (USAID, Unitaid) | Phase 3    DTG/FTC/TAF vs DTG/FTC/TDF vs EFV 600/FTC/TDF non-inferiority, open label    1050 treatment naive adult participants >12 years randomised 1:1:1  Johannesburg, South Africa | Establish non-inferior efficacy for DTG/FTC/ TAF compared to other study arms  Primary outcome number of participants with VL <50 copies/mL at 48 weeks  Secondary outcomes include: VL <50 copies/mL at 96 weeks, CD4 changes, tolerability, safety and efficacy | [Started January 2017](https://journals.lww.com/co-hivandaids/Fulltext/2017/07000/The_ADVANCE_study___a_groundbreaking_trial_to.8.aspx)  Fully recruited (May 2018)  Week 48 data available Q2 2019  Completion Q1 2020 |
| [NAMSAL](https://clinicaltrials.gov/ct2/show/NCT02777229) ANRS 12313  Inserm-ANRS  [(Unitaid)](https://unitaid.eu/news-blog/unitaid-anrs-launch-initiative-cameroon-bring-new-hiv-treatments-africa/#en) | Phase 3  DTG/3TC/TDF vs EFV400 mg /3TC/TDF non-inferiority, open label  606 treatment naive participants (303 per arm)  Yaoundé, Cameroon | Establish non-inferior efficacy for DTG/3TC/ TDF compared to EFV 400 mg/3TC/TDF  Primary outcome number of participants with VL <50 copies/mL at 48 weeks. Secondary outcomes include: VL <50 copies/mL at 24 weeks, CD4 changes, tolerability, safety and efficacy | Week 48 data expected HIV in Q4 2018 (Glasgow HIV Confernece 2018) |
| [ADVANZ-4](https://clinicaltrials.gov/ct2/show/NCT02337322)  Hospital Clinic of Barcelona | Phase 4  DTG/ABC/3TC vs DRV/r +ABC/3TC, randomised, open label  108 treatment naive participants with less than 100 CD4 cells/mm3  Barcelona, Spain | Compare immunological reconstitution and virological efficacy during 96 weeks in people with advanced HIV    Primary endpoint: median increase in CD4 cell count at 48 weeks | Completion Q4 2017 |

**Table 2: Dolutegravir pregnancy – key results to date**

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| --- | --- | --- | --- |
| **Study/cohort** | **Design** | **Purpose** | **Status** |
| [IMPAACT 1026s](https://clinicaltrials.gov/ct2/show/NCT00042289)  NIH (NIAID) | Phase 4  PK properties of antiretroviral and related drugs during pregnancy and PP  29 pregnant women >20 weeks gestation receiving DTG as part of clinical care  Washout PK in drug exposed infants  Multicountry: IMPAACT sites (United States, Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda) | Primary endpoint: PK 2nd /3rd trimester  Secondary endpoints: PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes | [Published in AIDS January 2018](http://i-base.info/htb/33540)  Exposure lower in pregnancy compared to PP with 50 mg once-daily dosing. Trough concentrations lower than in non-pregnant adults but above DTG EC90  2/29 anomalies (renal cysts) possibly related to DTG |
| [PANNA study](https://clinicaltrials.gov/ct2/show/NCT00825929)  [Radboud University (PENTA Foundation, ViiV Healthcare)](http://www.pannastudy.com/) | Phase 4  Pregnant women <33-week gestation receiving DTG as part of clinical care  Each study arm 16 with evaluable 33-week data  Multicountry: PANNA sites (Belgium, Germany, Ireland, Italy, Netherlands, Spain, UK) | Primary endpoint: PK at 33 weeks and 4–6 weeks after delivery  Secondary endpoints: PK in neonates, safety, VL and transmission | [Early results presented at 18th International Workshop on Clinical Pharmacology of Antiviral Therapy (June 2018)](http://i-base.info/htb/31795)  PK parameters in 3rd trimester comparable with those from the IMPAACT P1026s. But PP exposure higher in the IMPAACT study  [Unbound dolutegravir concentrations presented at 19th International Workshop on Clinical Pharmacology of Antiviral Therapy (June 2018)](http://i-base.info/htb/34349)  Unbound DTG plasma concentrations unchanged in pregnancy  Primary completion December 2020 |
| Tsepamo stud  Botswana | Observational cohort study  1729 PW who started DTG-based ART between 1 November 2016, and 30 September 2017  426 pre-conception exposures reported May 2018 | National birth surveillance: safety of ART in pregnancy | [Published in The Lancet Global Health June 2018](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30218-3/fulltext)  No significant differences by regimen in the individual outcomes of stillbirth, neonatal death, preterm birth, very preterm birth, SGA, or very SGA compared with to 4593 EFV exposed pregnancies  Preliminary data: 4/426 NTDs\*  Results from preconception substudy expected February 2019 |
| [EPPICC](http://penta-id.org/hiv/eppicc/)  European Pregnancy and Paediatric HIV Cohort Collaboration  PENTA | European observational cohort study | Epidemiological research on HIV positive pregnant women, children and children exposed to HIV in utero | [Results presented 9th International Workshop on HIV Paediatrics and IAS 2017 (July 2017)](http://i-base.info/htb/32182)  84/101 outcomes: 81 live births (83 newborns, two twin pregnancies), one spontaneous abortion, one induced abortion, and one stillbirth  58 1st trimester, 24 2nd, 18 3rd and one unknown earliest exposure  Abnormalities in 4/81 infants. (No pattern of defects and only infants and only 2 would be classified according to EUROCAT) |
| Antiretroviral Pregnancy Registry (APR) | Clinicians register pregnant women with prenatal exposure to any ARV before the pregnancy outcome is known, report data on exposure throughout pregnancy and provide birth outcome data | International (but largely US), registry that prospectively monitors prenatal ARV exposures to detect potential increases in the risk of birth defects | [Interim report results through 31 January 2018](http://www.apregistry.com/forms/interim_report.pdf)  No NTDs of 121 pre-conception exposures with outcomes  2 defects of 45 1st trimester and 96 2nd/3rd exposures |
| [DolPHIN1](https://clinicaltrials.gov/ct2/show/NCT02245022)  UoL (UCT, MU, LSTM, RU) | Phase 2  Pilot study of DTG PK in pregnant women in 3rd trimester and PP during 2 weeks BF  60 late presenting women (28–36 weeks gestation)    Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs    South Africa and Uganda | Primary endpoint: PK 3rd trimester  Secondary endpoints: safety and tolerability of DTG up to 2 weeks PP and VL at delivery | [Interim results CROI 2018 (March 2018)](http://www.croiconference.org/sessions/dolphin-1-dolutegravir-vs-efavirenz-when-initiating-treatment-late-pregnancy)  16 women – standard dose sufficient in 3rd trimester  [Results AIDS 2018](http://programme.aids2018.org/Abstract/Abstract/13144) (July 2018) |

\*[DTG started in pregnancy](http://viruseradication.com/journal-details/Safety_and_pharmacokinetics_of_dolutegravir_in_HIV-positive_pregnant_women:_a_systematic_review/) appears safe.

**But On 18 May 2018, the World Health Organisation (WHO) issued a statement following the identification of a potential safety issue with DTG related to neural tube defects (NTDs) in infants born to women who were taking DTG at the time of conception.**

The safety issue was found at a preliminary unscheduled analysis of Tsepamo, the ongoing observational study in Botswana that previously reported reassuring data on DTG started during pregnancy. The analysis revealed four cases of NTDs (spina bifida, anencephaly, encephalocele/iniencephaly) out of 426 women who became pregnant while taking DTG.

Work is ongoing to look at pregnancy timing/outcomes in early adopter and high-income country cohorts.

1. [WHO statement on DTG. 18 May 2018.](http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf)
2. [PEPFAR statement on potential safety issue affecting women living with HIV using dolutegravir at the time of conception. 18 May 2018.](https://www.pepfar.gov/press/releases/282221.htm)
3. [EMA press release. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir. 18 May 2018.](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1)
4. [US FDA. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). 18 May 2018.](https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm)
5. [Statement from the Southern African HIV Clinicians Society. 19 May 2018.](http://sahivsoc.org/Files/Dtg%20in%20Pregnancy%20Statement_1905.pdf)
6. [BHIVA statement on potential safety signal in infants born to women conceiving on dolutegravir. 22 May 2018.](http://i-base.info/htb/34205)
7. [GSK Dear Doctor letter. Tivicay (dolutegravir), Triumeq (dolutegravir, abacavir, lamivudine), Juluca (dolutegravir, rilpivirine): neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception. Ref: IE/DLG/0001/18. 22 May 2018.](http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information—tivicay-(dolutegravir)-triumeq-(dolutegravir-abacavir-lamivudine)-juluca-(dolutegravir-rilpivirine).pdf?sfvrsn=0)
8. [DHHS. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. 30 May 2018.](https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential)

**Table 3: Pregnancy dolutegravir – ongoing or planned\***

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| --- | --- | --- | --- |
| **Study** | **Design** | **Purpose** | **Status** |
| [DolPHIN2](https://clinicaltrials.gov/ct2/show/NCT03249181)  UoL (UCT, MU, LSTM, RU)  (Unitaid) | Phase 3  DTG PK, safety and efficacy in pregnant women in 3rd trimester and PP during BF until weaning or 18 months  250 late presenting women (28 weeks gestation to delivery)  Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs  South Africa and Uganda | Primary efficacy endpoint: proportion VL <50 at delivery  Primary safety endpoint: safety of DTG in pregnancy  Secondary: Time to UD VL, CD4 response, VL in breastmilk, genital HIV shedding, health economics, | Recruiting  Primary completion Q4 2021 |
| [VESTED](https://clinicaltrials.gov/ct2/show/NCT03048422)  [IMPAACT P2010](http://www.impaactnetwork.org/DocFiles/IMPAACT2010/IMPAACT2010_FINALv1.0_01DEC2016.pdf)  NIH (NIAID) | Phase 3  DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 639 mother/infant pairs  Treatment-naive women starting ART at 14–28 weeks gestation  50 weeks of maternal and infant follow-up PP    Multicountry: IMPAACT sites (US, Botswana, Brazil, Haiti, India, Malawi, South Africa, Tanzania,Thailand, Uganda, Zambia, Zimbabwe) | Primary endpoints: VL <200 copies/mL at delivery; adverse pregnancy outcomes; maternal toxicity; infant toxicity    Main secondary endpoints: VL <50 at delivery; VL <200 at 50 weeks PP; renal toxicity (mothers and infants); bone toxicity (subset of mothers and infants); adverse pregnancy outcomes; resistance (women with VF and HIV infected infants) | [Recruiting](http://impaactnetwork.org/DocFiles/P1026s/P1026sV9_22Sep14.pdf)  Primary completion December 2019  First results expected Q3 2019 |
| [ING200336](https://clinicaltrials.gov/ct2/show/NCT02075593)  PK and safety study in pregnant women with HIV  ViiV Healthcare | Phase 3  PK and safety single arm study of women with unintended pregnancies while participating in [ARIA](https://clinicaltrials.gov/ct2/show/NCT01910402) study of DTG/ABC/3TC FDC vs ATV/r +TDF/FTC in 474 treatment naive women to be completed in 2018  Estimated enrolment 25 women (approx 237 receive study drug in ARIA)  Multicountry: US, Russian Federation, Spain, UK | Primary endpoints: PK 2nd /3rd trimester    Secondary endpoints: PK in neonates, maternal:cord blood ratio, maternal and infant AEs; adverse pregnancy outcomes | Recruiting (started January 2015)  Primary completion February 2019 |

\*ADVANCE + NAMSAL also follow PW who become pregnant during the trials (NAMSAL switch from DTG to EFV arm but likely after the 28-day window for NTDs). Approx 40 DTG exposed across the two trials

**Table 4: Dolutegravir TB – ongoing or planned**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Design** | **Purpose** | **Status** |
| [INSPIRING](https://clinicaltrials.gov/ct2/show/NCT02178592)  ING117175  Open label study of DTG vs EFV for HIV/TB coinfection  ViiV | Phase 3  50 mg DTG twice daily vs 600 mg EFV (open label, randomised 3:2 ratio) during TB treatment  125 treatment naive participants  Multicountry: Argentina, Brazil, Mexico, Peru, Russian Federation, South Africa, Thailand | Establish antiviral activity of DTG or EFV containing regimens with TB treatment  Primary outcome number of participants with VL <50 copies/ mL at 48 weeks  Secondary outcomes include: VL <50 copies/mL at 24 weeks, CD4 changes, tolerability, safety and efficacy | [Week 24 data presented](http://www.croiconference.org/sessions/safety-and-efficacy-dolutegravir-based-art-tbhiv-coinfected-adults-week-24) (March 2018)  Week 24 results suggest DTG 50 mg twice daily seems effective and well-tolerated in HIV/TB co-infected adults receiving RIF-based TB therapy  [Week 48 data AIDS 2018 (July 2018)](http://programme.aids2018.org/Abstract/Abstract/6122) |
| [RADIO](https://clinicaltrials.gov/ct2/show/NCT03199690)  SSAT  (Wits University)  A clinical study investigating rifampicin and dolutegravir in combination in healthy volunteers | Phase 1  DTG 50 mg once daily with food for 1 week, PK day on day 7  Then DTG 100 mg once daily for 1 week, PK on day 14  Then 7-day wash out period  Start RIF on day 22 for 35 days and add DTG 50 mg on day 44, PK day on day 44  Then increase DTG to 100 mg once daily for another 7 days, PK on day 57  20 HIV negative participants  UK | Primary objective: investigate the PK of RIF 600 mg once daily and DTG 50 or 100 mg once daily in HIV negative participants  Secondary objective: investigate the safety and tolerability of RIF 600 mg once daily and DTG 50 or 100 mg once daily in HIV negative participants  Results will inform a bigger study that will be conducted in South Africa in people with HIV and TB who will be given rifampicin-containing regimens and DTG, ideally once daily | [Results presented at 19th International Workshop on Clinical Pharmacology (June 2018)](http://i-base.info/htb/34256)  DTG 100 mg once daily C24h reduced by 76% and 50 mg once daily by 85% vs DTG 50 mg alone    DTG C24h remained 2–14 fold above the in vitro protein adjusted IC90 in all participants |
| DTG 50 mg/RIF  UCT | Phase 2  Standard versus double dose DTG + RIF in HIV/TB coinfected participants  Viral load endpoints + PK | Establish whether standard 50 mg dose DTG can be used with RIF | Funding application stage |
| [IMPAACT 4TB](https://clinicaltrials.gov/ct2/show/NCT03435146)  Aurum Institute | Phase 1/2  Group 1: 1st 12 participants (Group 1a) PK DTG 50mg once daily + 2NRTIs + once weekly RPT/ INH  Next 18 participants (Group 1B) PK either DTG 50mg or a higher or more frequent dose, if adjustment is needed, + RPT/INH  Group 2: Next 30 participants will PK DTG as Group 1B  VL measured at protocol-defined intervals | PK, safety, and tolerability of once-weekly RPT/INH (3HP) for the treatment of latent tuberculosis infection in HIV + DTG-based ART | Recruiting  Estimated completion Q4 2018 |

**Tenofovir alafenamide**

Results from [a recent meta-analysis of TDF versus TAF](http://viruseradication.com/journal-details/Tenofovir_alafenamide_versus_tenofovir_disoproxil_fumarate:_is_there_a_true_difference_in_efficacy_and_safety%5E/) showed TDF, boosted with ritonavir or cobicistat, led to higher risks of bone and renal adverse events and lower rates of viral load suppression, compared with TAF. But, unboosted, there were no differences between the two versions of tenofovir for efficacy and only slight differences in safety.

TAF is being evaluated in ADVANCE (see first-line DTG table).

**Table 6: TAF pregnancy – ongoing or planned**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Design** | **Purpose** | **Status** |
| [IMPAACT 1026s](https://clinicaltrials.gov/ct2/show/NCT00042289)  NIH (NIAID) | Phase 4    PK properties of antiretroviral and related drugs during pregnancy and PP  Each arm 12–25 (target) women with evaluable 3rd trimester PK data  Pregnant women > 20 weeks gestation receiving TAF (3 arms –within FDCs) as part of clinical care  Washout PK in drug exposed infants  Multicountry: IMPAACT sites (United States, Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda) | Primary endpoint: PK 2nd /3rd trimester  Secondary endpoints: PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes | [Results AIDS 2018 (July 2018)](http://programme.aids2018.org/Abstract/Abstract/5960) |
| [PANNA study](https://clinicaltrials.gov/ct2/show/NCT00825929)  Radboud University (PENTA Foundation, ViiV Healthcare) | Phase 4  Pregnant women <33-week gestation receiving TAF as part of clinical care  Each study arm 16 with evaluable 33-week data  Multicountry: PANNA sites (Belgium, Germany, Ireland, Italy, Netherlands, Spain, UK) | Primary endpoint: PK at 33 weeks and 4–6 weeks after delivery  Secondary endpoints: PK in neonates, safety, VL and transmission | [Recruiting](http://www.pannastudy.com/main/inclusion)  3/16 recruited  Primary completion Dec 2020 |
| [VESTED](https://clinicaltrials.gov/ct2/show/NCT03048422)  [IMPAACT P2010](http://www.impaactnetwork.org/DocFiles/IMPAACT2010/IMPAACT2010_FINALv1.0_01DEC2016.pdf)  NIH (NIAID) | Phase 3  DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 639 mother/infant pairs  Treatment-naive women starting ART at 14–28 weeks gestation  50 weeks of maternal and infant follow-up PP    Multicountry: IMPAACT sites (US, Botswana, Brazil, Haiti, India, Malawi, South Africa, Tanzania,Thailand, Uganda, Zambia, Zimbabwe) | Primary endpoints: VL <200 copies/mL at delivery; adverse pregnancy outcomes; maternal toxicity; infant toxicity    Main secondary endpoints: VL <50 at delivery; VL <200 at 50 weeks PP; renal toxicity (mothers and infants); bone toxicity (subset of mothers and infants); adverse pregnancy outcomes; resistance (women with VF and HIV infected infants) | [Recruiting](http://impaactnetwork.org/DocFiles/P1026s/P1026sV9_22Sep14.pdf)  Primary completion December 2019  First results expected Q3 2019 |
| TAF switch study pregnancy  Wits RHI | Switch study evaluating PK, dosing and tolerability, pre- and post-switch from TDF (EFV/FTC/TDF FDC >3 months) to TAF 25 mg, through 6 months PP  26 women (and infants), 14-28 weeks gestation, stable (VL suppressed, tolerating well, no co-infection) on TDF-based ART | Primary endpoint: TFV-DP levels during pregnancy (baseline, 4 weeks post-switch, 2nd trimester, 3rd trimester) and PP (birth, 6–8 weeks)  Secondary endpoints: Tolerability, safety, VL outcomes of TAF, adverse, pregnancy outcomes, infant TFV-DP levels, infant safety PP, BM TFV-DP at 6 weeks and 6 months PP | Funding application stage  Earliest Q4 2019 (funding dependent) |

These pregnancy studies will not provide sufficient preconception data. Recent findings with dolutegravir and neural tube defects with exposure at conception are likely to make recommendations from WHO and national guidelines more cautious.

**Table 7: TAF TB – results to date + planned**

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| --- | --- | --- | --- |
| **Study** | **Design** | **Purpose** | **Status** |
| TAF twice daily/RIF PK    Gilead | Phase 1, open label, parallel design, multiple dose, single centre study  Twice-daily TAF 25 mg with once-daily RIF 600 mg vs once-daily TAF 25 mg (TAF as part of bictegravir/FTC/TAF FDC), 2 hours after food for 28 days  52 (26 per arm) HIV/TB negative participants | Evaluate TAF exposures with twice-daily administration to overcome drug-drug interaction with RIF | [Results presented at EACS 2017 (November 2017)](http://i-base.info/htb/32909)  **Twice-daily TAF plus RIF provided similar exposures to once-daily TAF**  Mean steady-state trough concentration of TFV-DP was above the historical steady state TFV-DP concentrations with TDF 300 mg |
| [RIFT](https://clinicaltrials.gov/ct2/show/results/NCT03186482)  The effect of rifampicin on the plasma pharmacokinetics of emtricitabine and tenofovir alafenamide fumarate and intracellular tenofovir-diphosphate and FTC triphosphate  SSCR101  SSAT  (Wits University, Gilead Sciences) | Phase 1 : TAF/FTC 25/200 mg once daily for 28 days (days 1–28)    Phase 2 : TAF/FTC 25/200 mg once daily plus RIF 600 mg once daily for 28 days (days 29–56)    Phase 3:  TDF 245 mg once daily for 28 days (days 57–84)  20 HIV/TB negative    UK | Primary  objective: PK of TAF, plasma tenofovir, Intracellular TFV-DP, FTC, and FTC-TP, during co-administration of TAF/FTC or TDF with RIF    Secondary  objective: safety and tolerability of the co-administered  drugs | [Results presented at CROI 2018 as LB (March 2018)](http://www.croiconference.org/sessions/rifampin-effect-tenofovir-alafenamide-taf-plasmaintracellular-pharmacokinetics)  RIF co-administration decreased plasma TAF by 55% and intracellular TFV-DP AUC by 36%, intracellular TFV-DP AUC were 76% higher with TAF + RIF than with TDF (300 mg once daily) alone\* |
| TAF/RIF PK  Wits/UCT  (Unitaid) | 30 HIV/TB-coinfected | TAF/RIF PK in HIV/TB coinfection | Protocol planning stage |

\*Two pharmacology (PK) studies in healthy volunteers suggest that TAF 25 mg could be given once daily with RIF. Both studies found the concentrations of TFV-diphosphate (DP) for TAF with RIF were higher than for people receiving standard TDF 300 mg.

**Second-line**

**Table 8: Second-line dolutegravir and darunavir/r – ongoing + planned**

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| --- | --- | --- | --- |
| **Study** | **Design** | **Purpose** | **Status** |
| [DAWNING](https://clinicaltrials.gov/ct2/show/NCT02227238) | Phase 3b  Open label study to evaluate the safety and efficacy of DTG + 2 NRTIs (genotype guided) vs LPV/r + 2 NRTIs in participants failing first-line NNRTI + 2 NRTIs.  624 participants  Multicountry: Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russian Federation, South Africa, Thailand, Ukraine | Primary endpoint: proportion with viral load <50 copies/mL at week 48 | [Week 24 data presented at IAS 2017 (July 2017)](http://i-base.info/htb/32241)  Independent Data Monitoring Committee (IDMC) conducted an ad hoc review of week 24 data  Recommended discontinuation of LPV/r arm due to differences in rates of virological nonresponse and increasing differences in rates of virological failure favouring the DTG arm  82% of participants on DTG vs 69% on LPV/r achieved viral load <50 copies/mL  [Week 48 data AIDS 2018](http://programme.aids2018.org/Abstract/Abstract/5633) ( July 2018)  Superior efficacy DTG arm |
| [Evaluation of low dose darunavir in a switch study](https://clinicaltrials.gov/ct2/show/NCT02671383)  WRHI052  Wits RHI  (USAID, MRC SA) | Phase 3  300 participants stable on LPV/r + 2 NRTI twice daily randomised to stay or switch to DRV/r 400/100 mg once daily  Primary endpoint VL <50 copies/mL at 48 weeks  Secondary endpoints include clinical and laboratory markers  48 weeks | 400/100 mg DRV/r is non-inferior to LPV/r in virologically suppressed participants  Primary endpoint VL <50 copies/mL at 48 weeks  Secondary endpoints include clinical and laboratory markers | [Week 48 data AIDS 2018](http://programme.aids2018.org/Abstract/Abstract/13192) (July 2018)  Non-inferior efficacy DRV/r 400/100 mg once daily arm |
| [D2EFT](https://clinicaltrials.gov/ct2/show/NCT03017872)  Kirby Institute  (Unitaid, US National Institute of Allergy and Infectious Disease, National Health and Medical Research Council, Australia) | Phase 3b/4  1,010 participants who failed first-line regimen randomised to DRV/r 800/100 mg + DTG vs DTG + 2 predetermined NRTIs vs DRV/r 800/100 mg + 2 NRTIs  96 weeks  Multicountry: Argentina, Brazil, Chile, Colombia, Mexico, Guinea, Mali, Nigeria, South Africa, Zimbabwe, India, Malaysia, Thailand, Indonesia | To compare two DTG-based second-line regimens with standard of care and with each other  Primary endpoint VL <50 at 48 weeks  Secondary endpoints include differences in VL using different thresholds, time to VL <50 copies, changes in baseline CD4 count | Recruiting  Primary completion December 2020 |
| NADIA  Coordinated by UoM | Phase 3  Approx 420 participants with virological failure on EFV-based 1st line randomised to DTG vs DRV/r once daily + (second factorial) TDF/XTC vs AZT/3TC | Compare DTG and DRV/r based regimens  Compare TDF/XTC vs AZT/backbone without genotype  Primary endpoint: VL <200 at 96 weeks  Interim analysis at 48 weeks | Protocol finalisation stage |

**Table 9: Additional darunavir/r studies**

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| DARifi  UCT  (USAID) | Safety of adjusted doses of DRV/r with rifampicin in HIV+ participants on PI-based ART | To compare steady state PK of DRV in 24 HIV+ (TB uninfected) participants given in standard DRV/r doses of 800/100 mg without rifampicin to:  1. DRV/r 1600/200 mg once daily with rifampicin  2. DRV/r 800/100 mg 12 hourly with rifampicin | Recruiting |
| DRV/r nanoformulation  UoL  (PEPFAR/USAID) | Preclinical evaluation in animal models | Lower overall dose of DRV (and potentially RTV) needed to achieve therapeutic steady state blood concentrations, using nanoparticles to improve drug absorption | Ongoing  Formulations on stability testing to establish shelf life for first-in-human studies in 2019 |

**Paediatrics**

A first-line regimen with DTG and TAF (plus XTC) has the potential to harmonise across age and weight bands and with adults.

**Dolutegravir**

**Table 11. Paediatric dolutegravir studies**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Design | Formulation(s) + dose | Status |
| Dolutegravir  [IMPAACT P1093](https://impaactnetwork.org/studies/P1093.asp)  ViiV Healthcare | Phase 1/2  Open label, PK, safety + efficacy  Approx 80 treatment-naive and -experienced participants aged 4 weeks to <18 years | 5 mg dispersible tablets  Approx 1 mg/kg with maximum dose of 50 mg to participants as per their age and weight band | 10 and 25 mg tablets approved for children and adolescents 6 years and above and weighing >30 kg US and >15 kg EU  [Data in >2 to <6 years age group presented ar CROI 2017 (July 2017)](http://www.croiconference.org/sessions/dolutegravir-pharmacokinetics-safety-and-efficacy-hiv-children-2)  DTG granules-in-suspension given at ~0.8 mg/kg once daily in >2 to <6 years old achieved target AUC24h. C24h was below the target but above the pharmacodynamic threshold in adults. These data inform dosing with dispersible tablets in this + younger cohorts.    Currently enrolling younger children and infants aged 4 weeks to <2 years (and also assessing WHO weight band dosing) |
| [ODYSSEY](https://clinicaltrials.gov/ct2/show/NCT02259127)  PENTA Foundation | Phase 2/3  Randomised non-inferiority trial of DTG-based regimens vs standard of care for first- and second-line  96 weeks  700 (310 first- + 390 second-line) participants Aged 6 months to 18 years, weighing >3 kg  Approx 60 extra younger children (3 lower weight bands: 3–6 kg, 6–10 kg, 10–14 kg)  South Africa, Uganda, Zimbabwe | Using originator + generic formulations  Making dosing practical  Aligning dosing to WHO weight bands (includes a PK sub-study to validate weight band dosing) | Main study enrolled  Recruitment opened to infants >3 kg + >6 months    Completion Q3 2019 |

**Tenofovir alafenamide**

TAF is being developed for children by the originator company Gilead Sciences in various fixed dose combination formulations

**Table 12: Paediatric TAF studies**

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| --- | --- | --- | --- |
| **Study** | **Design** | **Formulation/s and dose** | **Status and comments** |
| [Emtricitabine/tenofovir alafenamide](https://www.clinicaltrials.gov/ct2/show/NCT02285114)  (F/TAF)  Gilead | Phase 2/3  Open label switch study in 100 virologically suppressed participants aged 6 to <18 years stable on FTC/TDF plus 3rd agent  US, Panama, South Africa | 120/15mg FTC/TAF for children 17 to <25 kg  Non-solid formulation in development | FDA approved >12 years  6 to <18 years ongoing  Study in infants and children 4 weeks to <6 years planned |
| [Elvitegravir, cobicistat, emtricitabine, tenofovir alfenamide](https://www.clinicaltrials.gov/ct2/show/NCT01854775)    (E/C/F/TAF)  Gilead | Phase 2/3  Single arm, open label 48 week  100 E/C/F/TAF treatment-naive participants aged 6 to <18 years, weighing <25 kg  US, South Africa, Thailand, Uganda | Using adult formulation  Reduced dose FDC tablets in development | FDA approved >12 years  [TAF and its metabolite tenofovir (TFV) exposures are slightly higher in children aged 6–12 years compared with adults](http://www.croiconference.org/sessions/pharmacokinetics-safety-efficacy-ecftaf-hiv-infected-children-6-12-yrs)  Waiver <6 years |
| Rilpivirine, emtricitabine, tenofovir alafenamide  (R/F/TAF)  Gilead/  Janssen | Dependent on paediatric development of RPV and F/TAF | Reduced dose FDC tablets | FDA approved >12 years |
| [Bictegravir/emtricitabine/ tenofovir alafenamide](https://www.clinicaltrials.gov/ct2/show/NCT02881320)  (B/F/TAF)  Gilead | Phase 2/3  Open label switch study in 100 virologically suppressed participants aged 6 to <18 years  48 weeks  US, South Africa, Thailand, Uganda | Reduced dose FDCs | FDA approved >12 years  6 to <18 years ongoing  4 weeks to <6 years and/or <25 kg planned |

**Second-line**

**Table 13: Paediatric second-line study**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Design | Formulation/s | Status |
| [CHAPAS-4](http://www.ctu.mrc.ac.uk/our_research/research_areas/hiv/studies/chapas4/)  MRC CTU  (EDCTP) | PK and acceptability of second-line ART treatments in 1000 participants aged 3–15 years  VL>400 copies/ml, and failing first-line ART  DTG vs ATV/r vs DRV/r vs LPV/r plus TAF/XTC vs TDF/XTC (second factorial)  Uganda, Zimbabwe, Zambia | Originator + generic formulations | Planning stage  Recruitment starts August 2018 |

Key: ABC, abacavir; AIDS 2018, 22nd International AIDS Conference; ART, antiretroviral treatment; ARV, antiretroviral; ATV/r, atazanavir/ritonavir; BF, breastfeeding; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EDCTP, European and Developing Countries Clinical Trial Partnership; EFV, efavirenz; FDC, fixed dose combination; FTC, emtricitabine; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network; INH, isoniazid; LPV/r, lopinavir/ritonavir; LSTM, Liverpool School of Tropical Medicine; MCC SA, Medicines Control Council South Africa; MRC, CTU, Medical Research Council Clinical Trials Unit; MU, Makerere University; NIH, US National Institutes of health; NTDs, neural tube defects; PK, pharmacokinetic; PP, postpartum; PTD, preterm delivery; PW, pregnant women; RIF, rifampicin: RPT, rifapentine; RU, Raboud University; SGA, small for gestational age; SoC, standard of care; SSAT, St Stephens AIDS Trust; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TM, trimester; UCT, University of Cape Town; UoL University of Liverpool;; UNSW, University of New South Wales; VL, viral load; Wits RHI, The Wits Reproductive Health and HIV Institute; XTC, lamivudine or emtricitabine; 3TC, lamivudine