# INSPIRING: SAFETY AND EFFICACY OF DOLUTEGRAVIR-BASED ART IN TB/HIV CO-INFECTED ADULTS

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# Rifampicin

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# Rifapentine

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# HIV and Tuberculosis Epidemiology

## Global Burden of Tuberculosis, 2017

| | Total Population | HIV-Infected Persons |
|---|---|---|
| Incidence | 10.0 million | 900,000 (9%) |
| Deaths | 1.3 million | 300,000 (23%) |

Limited treatment options:

- Drug interactions
- Overlapping toxicities
- IRIS

WHO Report 2018 Global Tuberculosis Control

# Global roll-out of dolutegravir (DTG)

## ROLE OF NEW ARV OPTIONS IN 2016 WHO GUIDELINES

| ARV | Population | 1st line | 2nd line | 3rd line | Comments |
|---|---|---|---|---|---|
| $EFV_{400}$ | Adult/Adol | ✓ | | | • dose reduction in children is not needed (already pK adjusted). |
| **DTG** | Adult/Adol | ✓ | | ✓ | • **Twice daily dose probably needed in patients using rifamycins** |

## MAJOR CLINICAL AND PROGRAMMATIC CHALLENGES WITH NEW ARVS

| Drug | Gaps in safety & efficacy (specific populations) | Gaps on how to promote programmatic transition | Limitations on drug regulations, formulations and price | Expected availability of generic formulations | Potential actions to address the knowledge gaps |
|---|---|---|---|---|---|
| **DTG** | ✓ | ✓ | | 2017/2018 | • Clinical & pK studies (Pregnant women, **TB**, children)<br>• Pharmacoeconomic studies |
| **TAF** | ✓ | | | 2019 | • Clinical & pK studies Pregnant women, **TB**, children, PreP |

Adapted from Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance. Geneva: World Health Organization; 2018 (WHO/CDS/HIV/18.18). Licence: CC BY-NC-SA 3.0 IGO.

# Listening to the patients

## Communique of the Kigali Dolutegravir Stakeholder Meeting of African Women Living with HIV, hosted by AfroCAB

We, the thirty-nine women living with HIV representing 18 countries, met in Kigali on July 13 and 14 to discuss the potential neural tube defect (NTD) safety signal in women taking dolutegravir (DTG) at conception and develop a joint position on behalf of women for access to optimal HIV treatment and prevention.

### Key Outcomes

**Discussion**

We deliberated on the potential safety signal data from the Botswana Tsepamo study and **determined unanimously based on the data currently available that DTG's benefits – reduced side effects, improved efficacy, and a high barrier to resistance – outweigh its potential risks.**

Although this decision was reached unanimously, DTG, like all ARVs, has associated risks of side

***"On TLE, I felt dizzy, tired, couldn't work, and couldn't take care of my small kids properly. It's been one month since I started using it [DTG]. It's a big change. I'm active, my kids are happy because they have an active mother, and I can do my work without depending on anybody."***

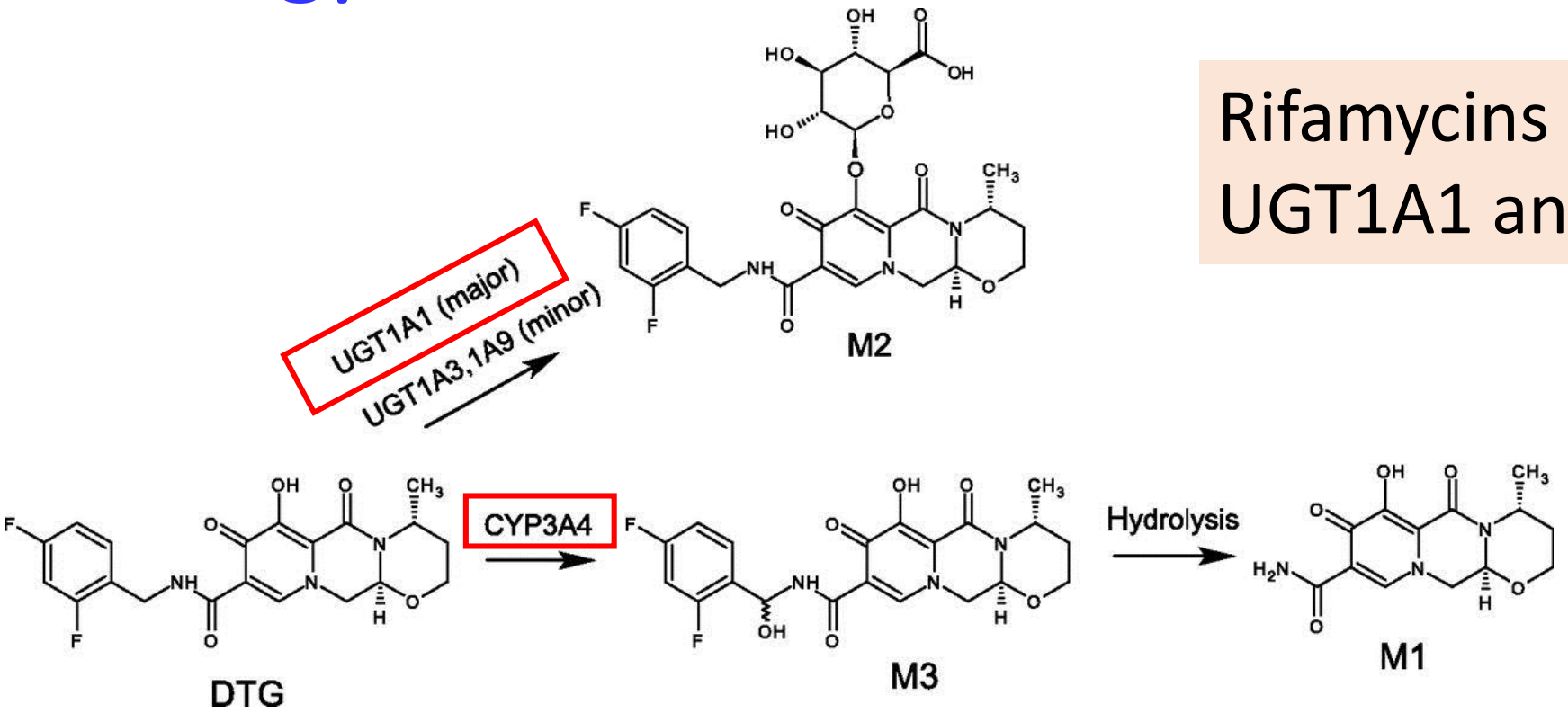
**As a result of these struggles, and the lack of conclusive evidence linking DTG to increased risk of NTDs, we, the women living with HIV at this meeting, concluded that blanket exclusions that deny women equitable access to this optimal HIV treatment are not warranted or justified.** The

IAS2018: Communique of the Kigali Dolutegravir Stakeholder Meeting of African Women Living with HIV, hosted by AfroCAB

# Can we use DTG to treat HIV in patients with HIV-TB Co-Infection?

- Is it safe?
- What's the right dose?
- Does it work?

# Pharmacology of DTG

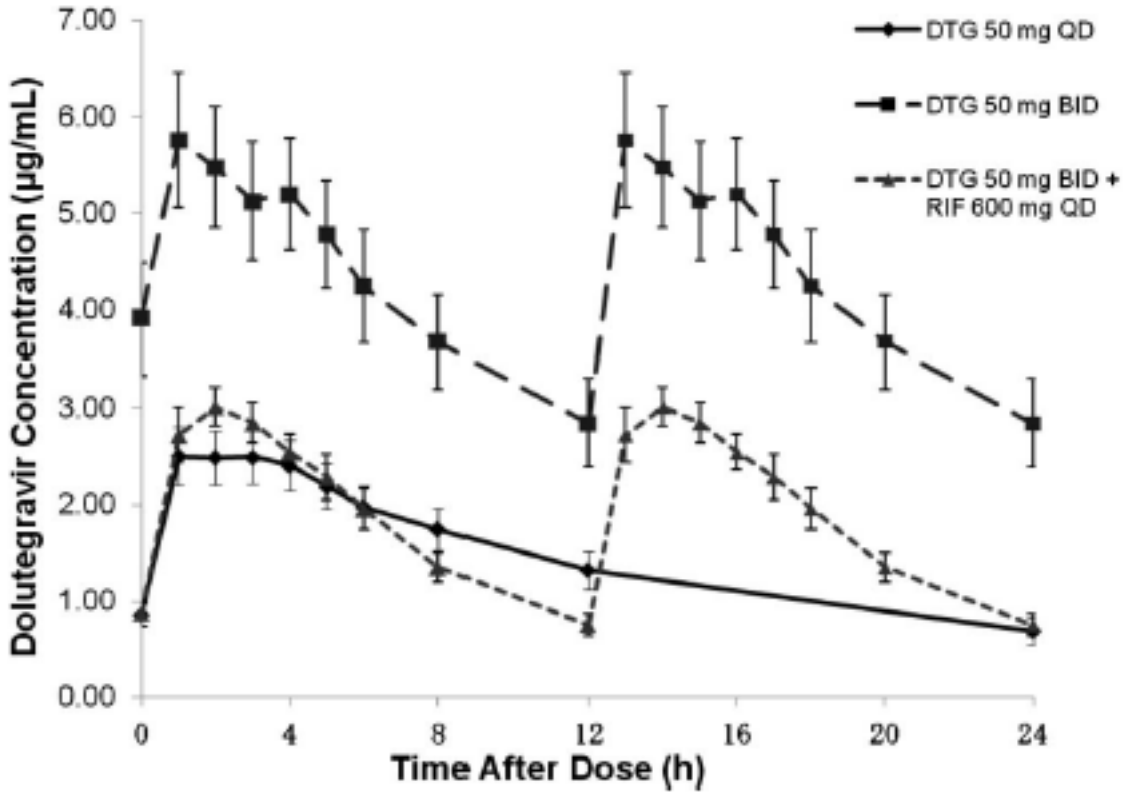



Rifamycins induce both UGT1A1 and CYP3A4

- How much DTG do we need? What is the target?
  - Target exposure should be greater than the trough concentration ($C_T$) observed at 10 mg once daily (0.30 mcg/mL)
  - Equivalent to the $EC_{90}$ based on $E_{max}$ model from PK/PD analysis of monotherapy study
  - With 50 mg daily, $C_T$ is 1.20 mcg/mL; 0.30 mcg/mL is 25% of that value
  - Requirement that boundaries of the 90% GMR (comparing DTG alone vs. DTG with companion drug) does not fall below 0.25 for the drug interaction

SPRING-1 Van Lunzen Lancet ID 2012; Reese et al Drug Metab Disp (2013) 41: 353.

# DTG with RIF or RBT- healthy volunteers

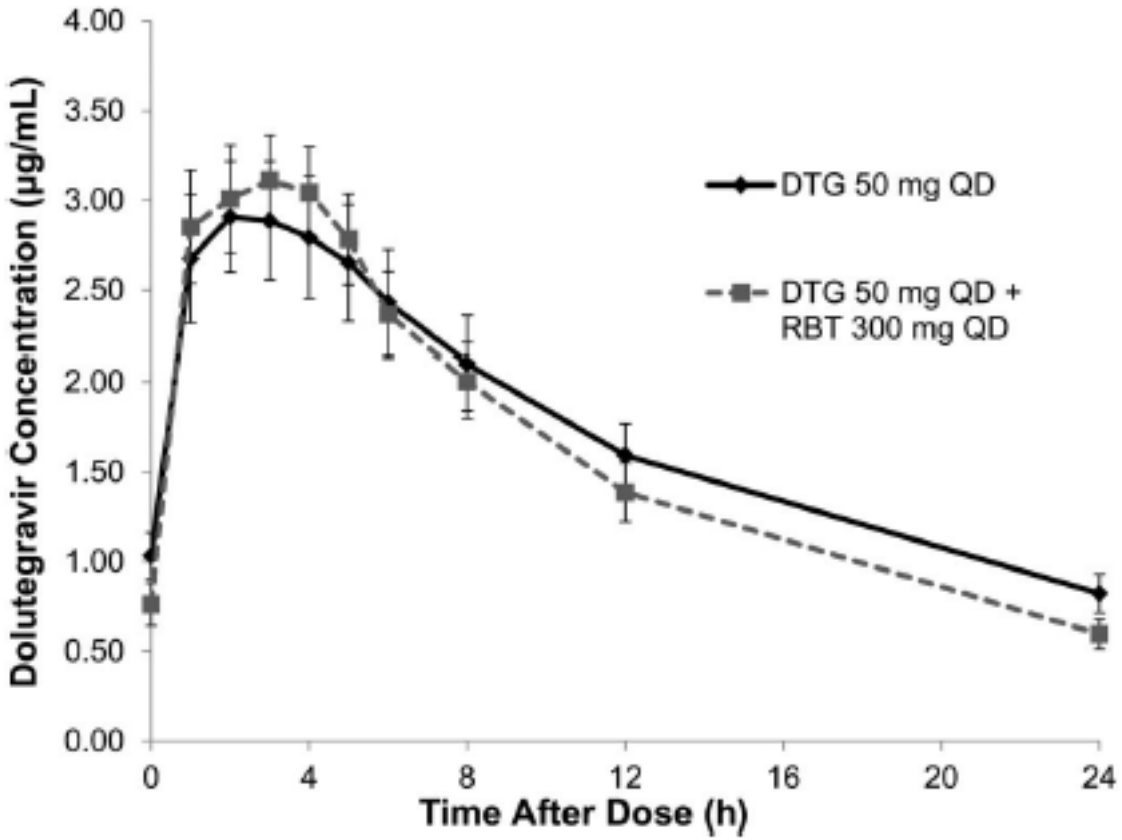



**Rifampin+DTG BID vs. DTG QD alone**

GMR $AUC_{0\text{-}24}$: 1.33 (1.15 to 1.53)

GMR $C_T$: 1.22 (1.01 to 1.48)

*Well-tolerated*




**Rifabutin+DTG QD vs. DTG QD alone**

GMR $AUC_{0\text{-}24}$: 0.95 (0.82 to 1.10)

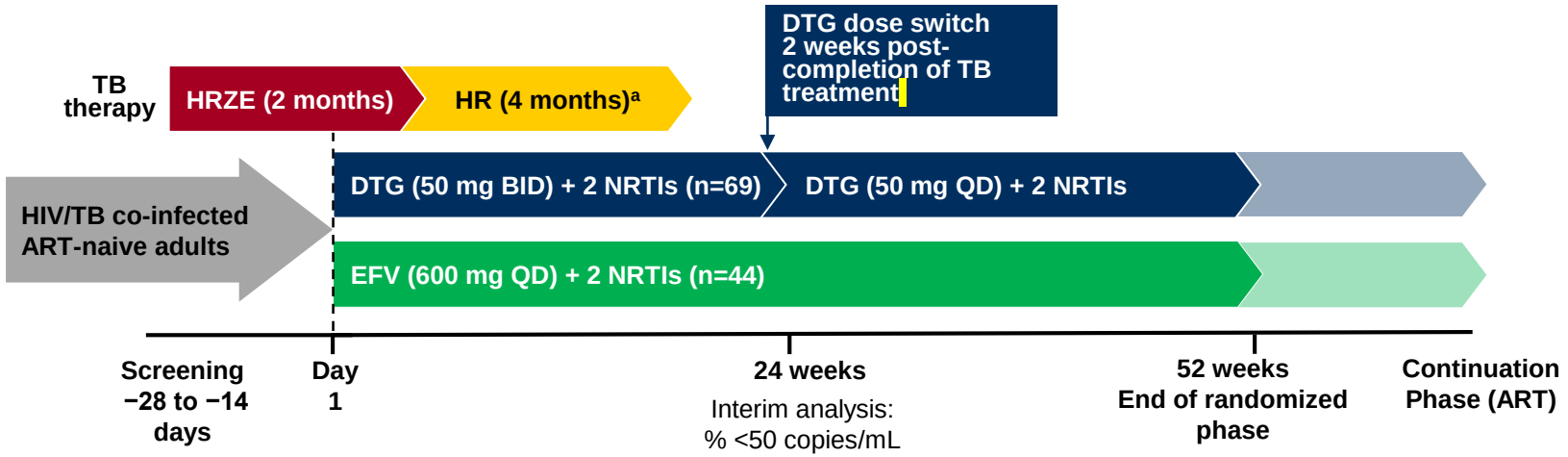
GMR $C_T$: 0.70 (0.57 to 0.87)

*One participant with rifamycin hypersensitivity*

JAIDS (2013) 62: 21.

# INSPIRING: Phase IIIb Study Design

**Phase IIIb, randomized, multicenter, open-label, non-comparative, active-controlled, parallel-group study**




**Inclusion criteria**

- HIV-1 RNA ≥1000 copies/mL and CD4+ ≥50 cells/mm$^3$
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomization and no later than the screening date

**DTG:EFV 3:2 randomization stratified by**

- Screening plasma HIV-1 RNA ≤100,000 or >100,000 copies/mL
- Screening CD4+ ≤100 or >100 cells/mm$^3$

[a]Duration of continuation phase of TB treatment according to local guidelines (up to 7 months in some countries).
ClinicalTrials.gov, NCT02178592.

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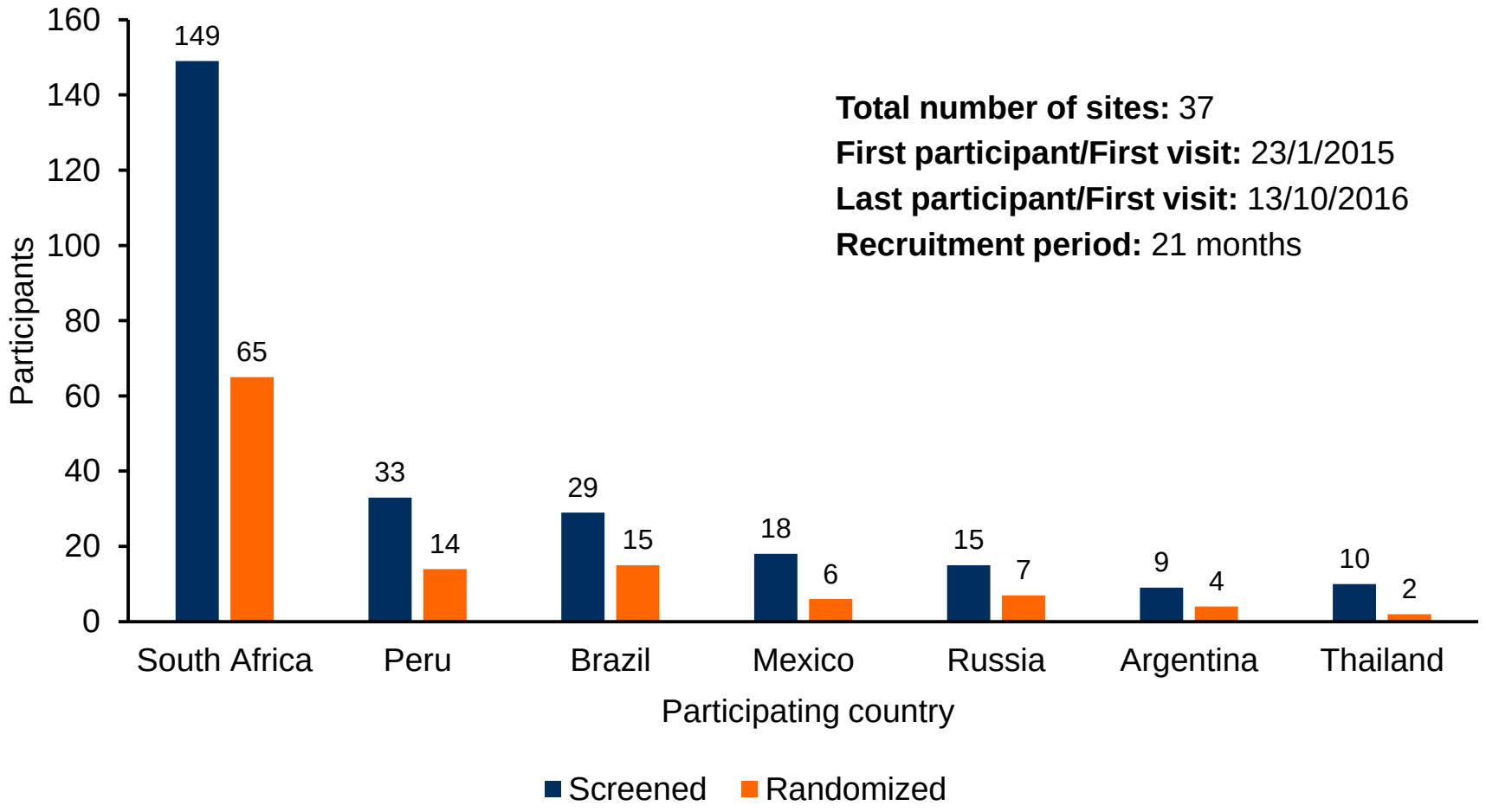
# Study Endpoints

- **Primary Endpoint**
  - Proportion of DTG-treated participants with **plasma HIV-1 RNA <50 copies/mL at Week 48** using the modified FDA snapshot algorithm[a] in the ITT-E population
- **Secondary Endpoints**
  - Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24 using the modified FDA snapshot algorithm[a] in the ITT-E population
  - Proportion of EFV-treated participants with plasma HIV-1 RNA <50 copies/mL at Week 48 using the modified FDA snapshot algorithm[a] in the ITT-E population
  - Changes from baseline in **CD4+** cell counts at Week 24 and Week 48
  - Incidence and severity of all **AEs**, SAEs, and laboratory abnormalities
  - Proportion of participants with TB- and non–TB-associated **IRIS** as assessed by the IRIS independent adjudication panel
  - Incidence of treatment-emergent genotypic and phenotypic **resistance** to DTG, EFV, and other on-study ART in participants meeting **confirmed virologic withdrawal criteria**
- **Tertiary Endpoint**
  - TB treatment success (using the WHO definition [2014])

[a]Modified FDA snapshot: NRTI switch for tolerability not counted as failure.

# INSPIRING Global Enrollment (N=113)




**Total number of sites:** 37
**First participant/First visit:** 23/1/2015
**Last participant/First visit:** 13/10/2016
**Recruitment period:** 21 months

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# Demographic and Baseline Characteristics

| | DTG (n=69) | EFV (n=44) |
|---|---|---|
| **Age, median (range), years** | 33 (18-62) | 32 (20-50) |
| ≥50 years, n (%) | 9 (13) | 2 (5) |
| **Female, n (%)** | 30 (43) | 16 (36) |
| **African heritage/African, n (%)** | 47 (68) | 29 (66) |
| **HIV-1 RNA, median (Q1, Q3), $log_{10}$ copies/mL** | 5.10 (4.74, 5.47) | 5.24 (4.50, 5.67) |
| >100,000 copies/mL, n (%) | 44 (64) | 24 (55) |
| **CD4+ cell count, median (Q1, Q3), cells/mm$^3$** | 208 (128, 410) | 202 (92, 354) |
| ≤100 cells/mm$^3$, n (%) | 13 (19) | 12 (27) |
| **Current TB conditions, n (%)[a]** | | |
| Pulmonary TB | 65 (94) | 44 (100) |
| Lymph node TB | 5 (7) | 2 (5) |
| Pleural TB | 5 (7) | 0 |
| **Time from start of TB therapy to Day 1, median (Q1, Q3), days** | 35.0 (28.0, 44.0) | 33.5 (26.0, 50.5) |
| **Most common NRTI backbone, n (%)** | | |
| TDF/FTC | 46 (67) | 31 (70) |
| TDF/3TC | 4 (6) | 3 (7) |

[a]Participants could have had pulmonary TB with pleural or lymph node TB.

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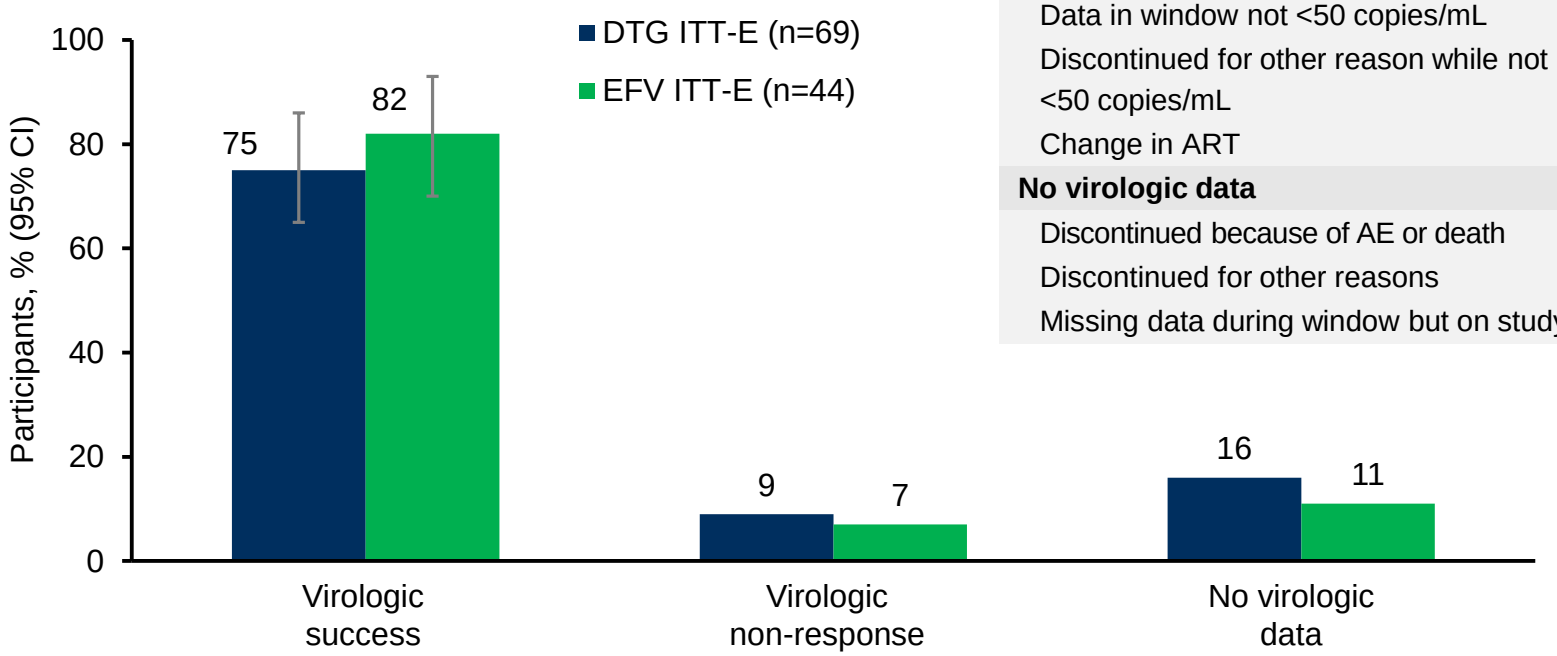
# Modified FDA Snapshot Outcomes at Week 48




| n (%) | DTG (n=69) | EFV (n=44) |
|---|---|---|
| **Virologic success (HIV-1 RNA <50 copies/mL)** | **52 (75)** | **36 (82)** |
| **Virologic nonresponse** | **6 (9)** | **3 (7)** |
| Data in window not <50 copies/mL | 0 | 2 (5) |
| Discontinued for other reason while not <50 copies/mL | 6 (9)[a] | 1 (2)[b] |
| Change in ART | 0 | 0 |
| **No virologic data** | **11 (16)** | **5 (11)** |
| Discontinued because of AE or death | 0 | 2 (5)[c] |
| Discontinued for other reasons | 11 (16)[d] | 3 (7)[e] |
| Missing data during window but on study | 0 | 0 |

[a]DTG: discontinued for other reasons while not <50 copies/mL: 3 lost to follow-up (Days 192, 255, 337); 2 withdrawal of consent (Days 118, 253); 1 pregnancy (Day 256).
[b]EFV: discontinued for other reasons while not <50 copies/mL: 1 lost to follow-up (Day 2).
[c]EFV: discontinued due to AE: 1 EFV hypersensitivity; 1 increased gamma-glutamyltransferase.
[d]DTG: No virologic data/Discontinued for other reasons: 7 lost to follow-up (25, 80, 177, 181, 223, 268, 326); 2 pregnancies (D253, 305); 1 physician decision (misdiagnosis TB Rx failure); 1 withdrawal of consent (Day 116).
[e]EFV: No virologic data/Discontinued for other reasons: 2 lost to follow-up (Days 177, 296); 1 withdrawal of consent (patient relocated).

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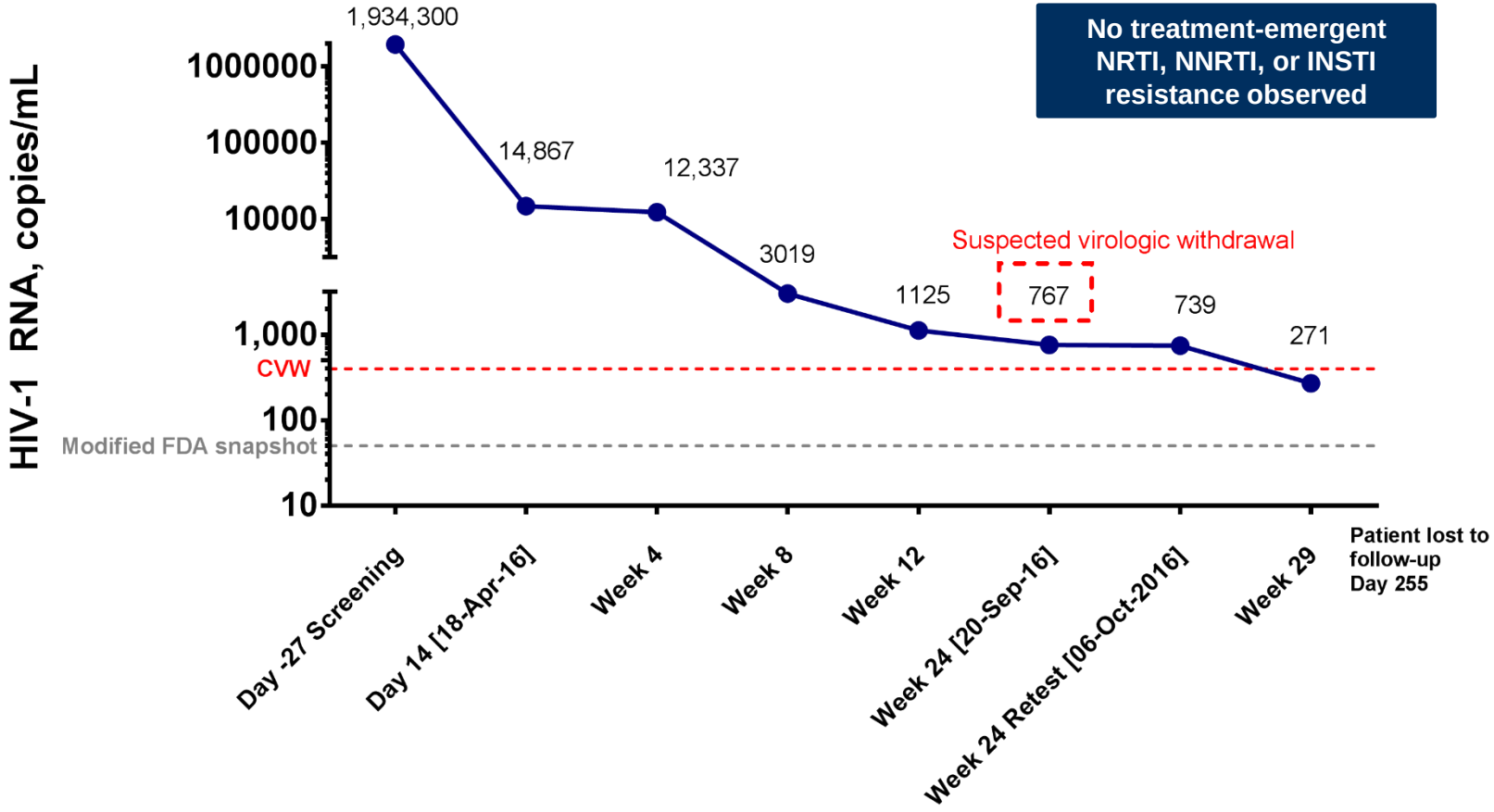
# Participants With Confirmed Virologic Withdrawal

- **50-year-old male participant randomized to DTG**
  - NRTI background regimen: ddI/3TC
  - Baseline viral load: 1,934,300 copies/mL

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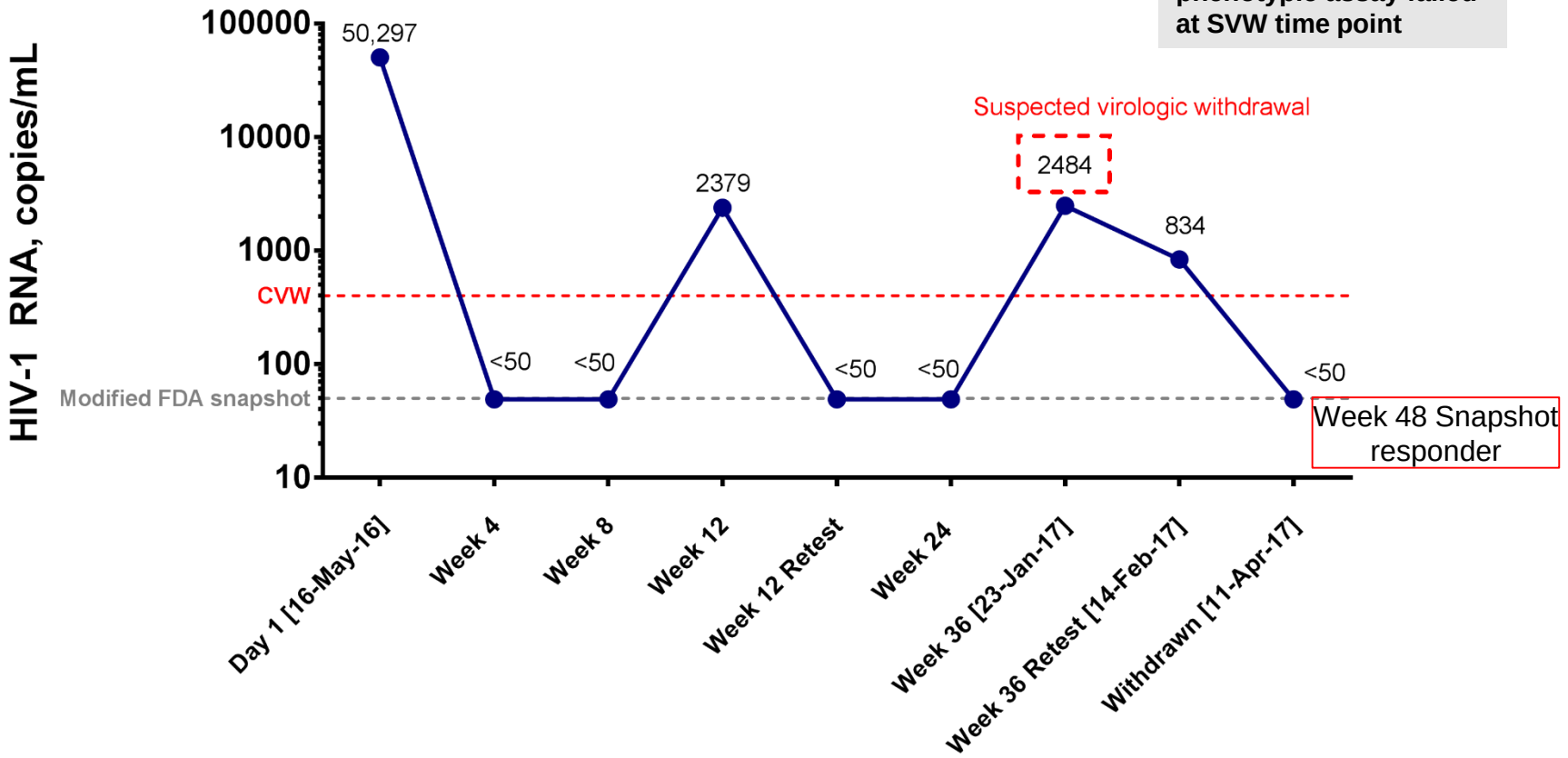
# Participants With Confirmed Virologic Withdrawal (cont)

- **36-year-old male participant randomized to DTG**
  - NRTI background regimen: TDF/FTC
  - Study drug nonadherence reported Weeks 11-12 and Weeks 18-20

**No NRTI or NNRTI treatment-emergent resistance observed**

**Integrase genotypic/ phenotypic assay failed at SVW time point**

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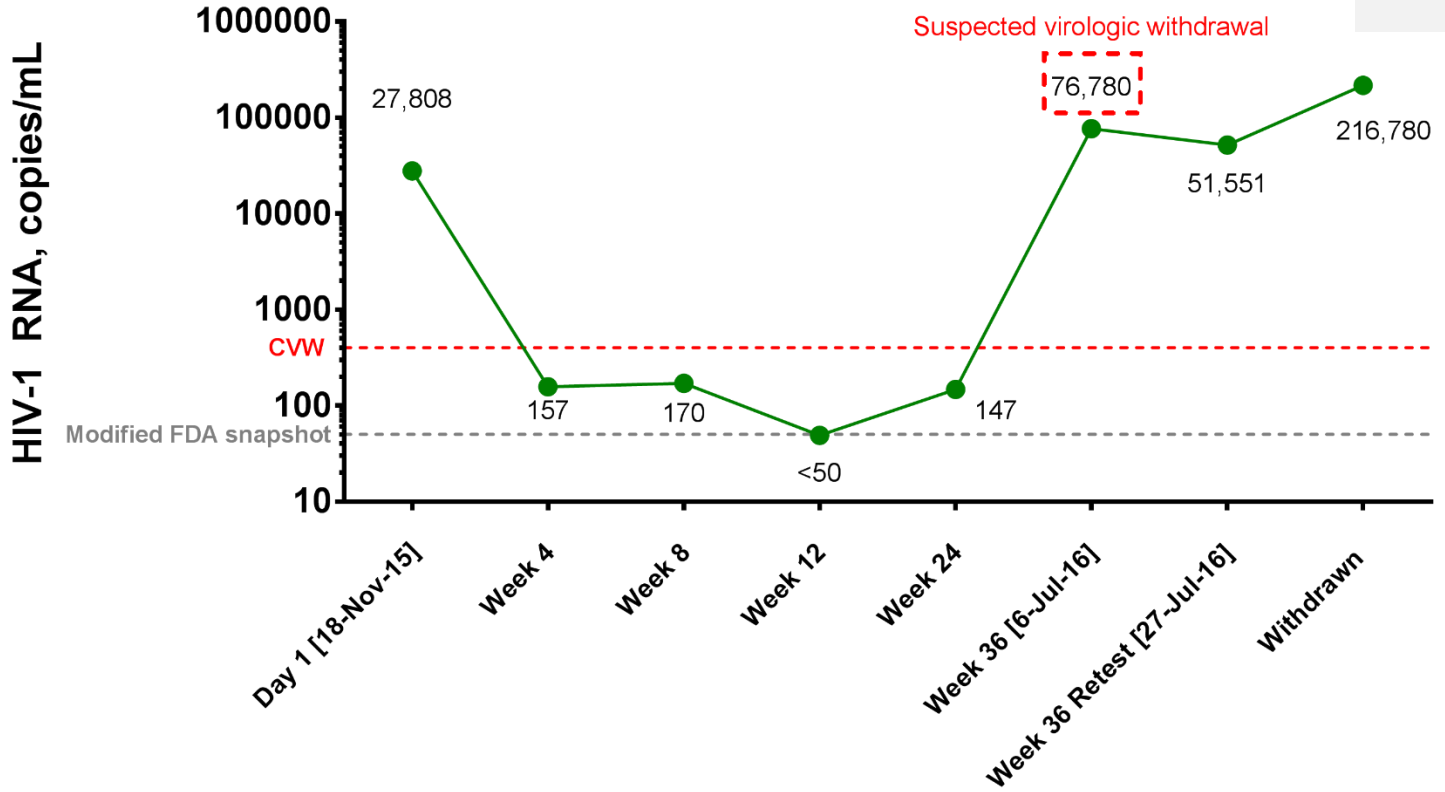
# Participants With Confirmed Virologic Withdrawal (cont)

- **26-year-old male participant randomized to EFV**
  - NRTI background regimen: TDF/FTC
  - Treatment-emergent NRTI and NNRTI resistance observed
  - No treatment-emergent INSTI resistance observed

| Class | Mutation |
|---|---|
| NRTI | K65R |
| NNRTI | K101E, K103K/N, V106M, Y181Y/C, G190G/A |

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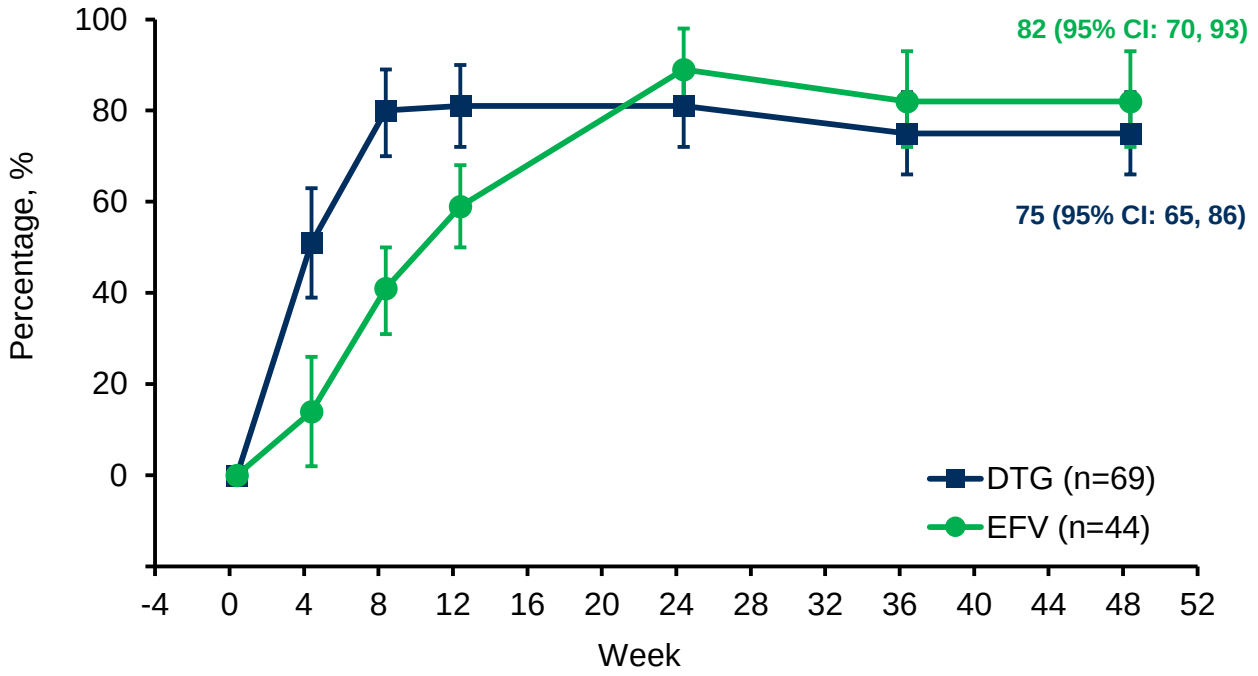
# Virologic and Immunologic Results in the ITT-E Population in Randomized Phase

**Modified FDA Snapshot Analysis (ITT-E)**

Proportion of participants with HIV-1 RNA <50 copies/mL (95% CI)




**INSPIRING pharmacokinetic data**

| Pre-dose concentration: DTG 50 mg BID with TB treatment | | |
|---|---|---|
| **Time** | **n** | **DTG $C_T$ (ng/mL) geometric mean (%CVb)** |
| Week 8 | 42 | 870 (118) |
| Week 24 | 23 | 964 (263) |

| Pre-dose concentration: DTG 50 mg QD (post-TB treatment phase) | | |
|---|---|---|
| **Time** | **n** | **DTG $C_T$ (ng/mL) geometric mean (%CVb)** |
| Week 36 | 27 | 854 (208) |
| Week 48 | 26 | 881 (281) |

DTG $C_{tau}$, when administered twice daily with RIF, was similar to DTG 50 mg once daily without RIF and to previously reported data for DTG 50 mg once daily in phase II/III HIV trials

- Median change from baseline in CD4+ cell count (Q1, Q3) at Week 48
  - DTG, 220 cells/mm$^3$ (111, 271)
  - EFV, 190 cells/mm$^3$ (104, 252)

[a]Modified FDA snapshot: NRTI switch for tolerability not counted as failure.

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# TB Treatment Outcomes

| n (%) | DTG (n=69) | EFV (n=44) |
|---|---|---|
| **Treatment Success** | **61 (88)** | **40 (91)** |
| Treatment failure | 0 | 1 (2) |
| Died | 0 | 0 |
| Not evaluated / Lost to follow-up | 8 (12) | 3 (7) |

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# Adverse Events in Randomized Phase

| n (%) | DTG (n=69) | EFV (n=44) |
|---|---|---|
| **Any AE** | **52 (75)** | **40 (91)** |
| **AEs occurring in ≥10% of participants in either group** | | |
| Headache | 9 (13) | 6 (14) |
| Upper respiratory tract infection | 5 (7) | 8 (18) |
| Lower respiratory tract infection | 9 (13) | 3 (7) |
| Diarrhea | 3 (4) | 10 (23) |
| Dizziness | 3 (4) | 6 (14) |
| Arthralgia | 7 (10) | 0 |
| Gastroenteritis | 1 (1) | 5 (11) |
| **Any serious AE (SAE)** | **5 (7)** | **5 (11)** |
| Drug-related SAEs[a] | 1 (1) | 1 (2) |
| **Any drug-related AE** | **19 (28)** | **14 (32)** |
| Grade 1-2 | 16 (23) | 12 (27) |
| Grade 3 | 2 (3) | 1 (2) |
| Grade 4 | 1 (1) | 1 (2) |
| **AEs leading to withdrawal** | **0** | **2 (5)[b]** |
| **Any psychiatric AE** | **5 (7)** | **6 (14)** |
| Grade 1-2 | 5 (7) | 6 (14) |
| Grade 3-4 | 0 | 0 |
| SAEs | 0 | 1 (2)[c] |

[a] One TB-associated IRIS in each arm. [b] One EFV hypersensitivity and one gamma-glutamyltransferase elevation.
[c] Suicidal ideation considered unrelated to study drug and resolved the same day.

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# TB- and Non–TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS)

| n (%) | DTG (n=69) | EFV (n=44) |
|---|---|---|
| **Participants with events sent to adjudication committee for TB-associated IRIS** | **9 (13)** | **12 (27)** |
| Met criteria for TB-associated IRIS | 4 (6)[a] | 4 (9)[b] |
| Possibly met criteria for TB-associated IRIS | 0 | 0 |
| **Participants with events sent to adjudication committee for non–TB-associated IRIS** | **2 (3)** | **3 (7)** |
| Met criteria for non–TB-associated IRIS | 1 (1)[c] | 0 |
| Possibly met criteria for non–TB-associated IRIS | 1 (1)[d] | 0 |

**No participant in either arm permanently discontinued treatment because of IRIS**

[a]1 × Grade 1, 2 × Grade 2, and 1 × Grade 3. [b]3 × Grade 2 and 1 × Grade 4.

[c]Grade 2 (IRIS and strongyloidiasis; also experienced TB-associated IRIS). [d]Grade 1 (herpes zoster).

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# Participants With Liver Chemistry Abnormalities in Randomized Phase

| Maximum postbaseline emergent toxicity,[a] n (%) | DTG (n=69) | EFV (n=44) |
|---|---|---|
| ALT ≥3 to <5 × ULN | 0 | 1 (2) |
| ALT ≥5 to <10 × ULN | 1 (1) | 1 (2) |
| ALT ≥10 × ULN | 0 | 0 |

**No AEs meeting stopping criteria for drug-induced liver injury in either group**

[a]Participants were summarized on the basis of maximum postbaseline value. Participants with missing baseline data were assumed to be normal at baseline.

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# Conclusions

- DTG 50 mg BID during concomitant RIF-based TB therapy demonstrated efficacy and strong immunologic response through Week 48
  - ITT-E population: DTG, 75% (95% CI, 65%, 86%); EFV, 82% (95% CI, 70%, 93%)
  - 2 CVW on DTG with no treatment-emergent resistance-associated mutations (RAMs) detected; 1 CVW on EFV with treatment-emergent RAMs
  - 11 (16%) nonresponders by FDA snapshot in the DTG group discontinued for non–treatment-related reasons while suppressed (mainly lost to follow-up)
  - DTG $C_{tau}$ with twice-daily administration of DTG 50 mg with RIF was similar to that of once-daily DTG 50 mg without RIF
- DTG was well tolerated; the majority of AEs were Grade 1 or 2, with low rates of drug-related AEs and serious AEs and no AEs leading to withdrawal
  - Low rates of TB- and non–TB-associated IRIS in both groups; none led to discontinuation
  - No AEs meeting the stopping criteria for drug-induced liver injury in either group
- TB treatment success high (~90%) in both groups
- This study provides support for use of DTG in patients with HIV-associated TB requiring RIF-based TB treatment and effective ART

# WHO July 2018 Updated ART guidelines




**BOX 1. RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS**

1. A DTG based regimen may be recommended as a preferred first-line regimen for people living with HIV initiating ART *(conditional recommendation)*
   - Adults and adolescents *(moderate-certainty evidence)*
   - Women and adolescent girls of childbearing potential[a] *(very-low-certainty evidence)*
   - Infants and children with approved DTG dosing[b] *(low-certainty evidence)*

**BOX 3. A WOMAN-CENTRED APPROACH**

Woman-centred health services involve an approach to health care that consciously adopts the perspectives of women and their families and communities. This means that health services see women as active participants in and beneficiaries of trusted health systems that respond to women's needs, rights and preferences in humane and holistic ways. Care is provided in ways that respect women's autonomy in decision-making about their health, and services must provide information and options to enable women to make informed choices. The needs and perspectives of women, their families and communities are central to providing care and to designing and implementing programmes and services. A woman-centred approach is underpinned by two guiding principles: promoting human rights and promoting gender equality.

Source: *Consolidated guideline on sexual and reproductive health and rights of women living with HIV (3).*

Recent data on the efficacy and safety of DTG co-administered with rifampicin among people coinfected with HIV and TB showed that the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin. This extra dose of DTG was well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared with EFV.

http://www.who.int/hiv/pub/guidelines/ARV2018update/en/

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Coming soon…

# DOLPHIN: Dolutegravir and 3HP in patients with LTBI & HIV

## *Study design*

**Design**: Single-arm Phase I/II PK and safety study of DTG-based ART and once-weekly rifapentine plus isoniazid (3HP) in adults with HIV infection (on ART with suppressed viral load) who have indication for treatment of LTBI

**Regimens**: Group 1A: DTG 50mg daily + TDF/FTC +3HP (900/900) → interim analysis

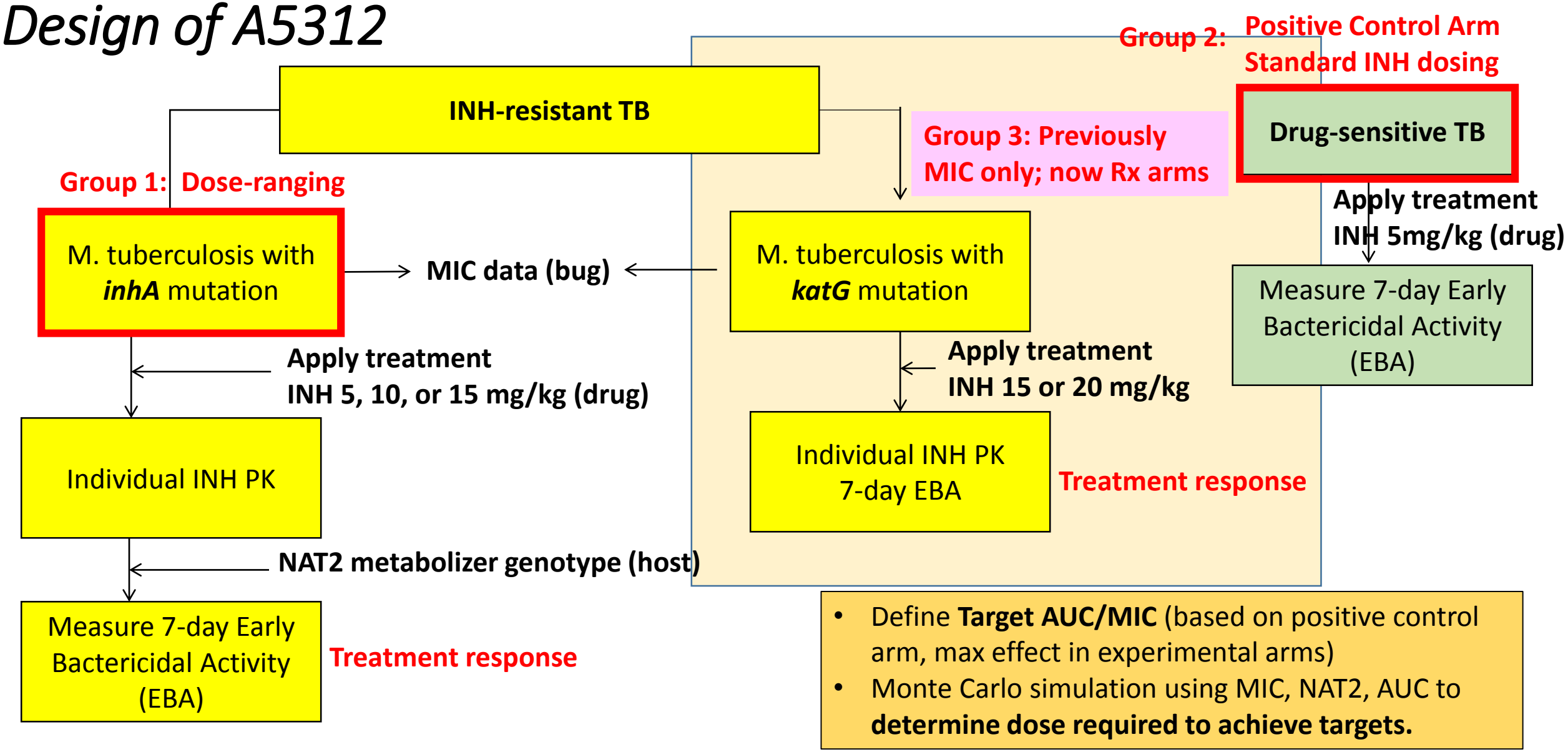
Group 1B and 2: DTG, dose TBD, + TDF/FTC + 3HP

**Duration**: 8 weeks DTG+TDF/FTC (EFV washout); 12 weeks DTG+TDF/FTC+HP; post-treatment DTG access 12 months

**Sample size**: 60 (30 in Group 1 (12 in 1A, 18 in 1B), 30 in Group 2)

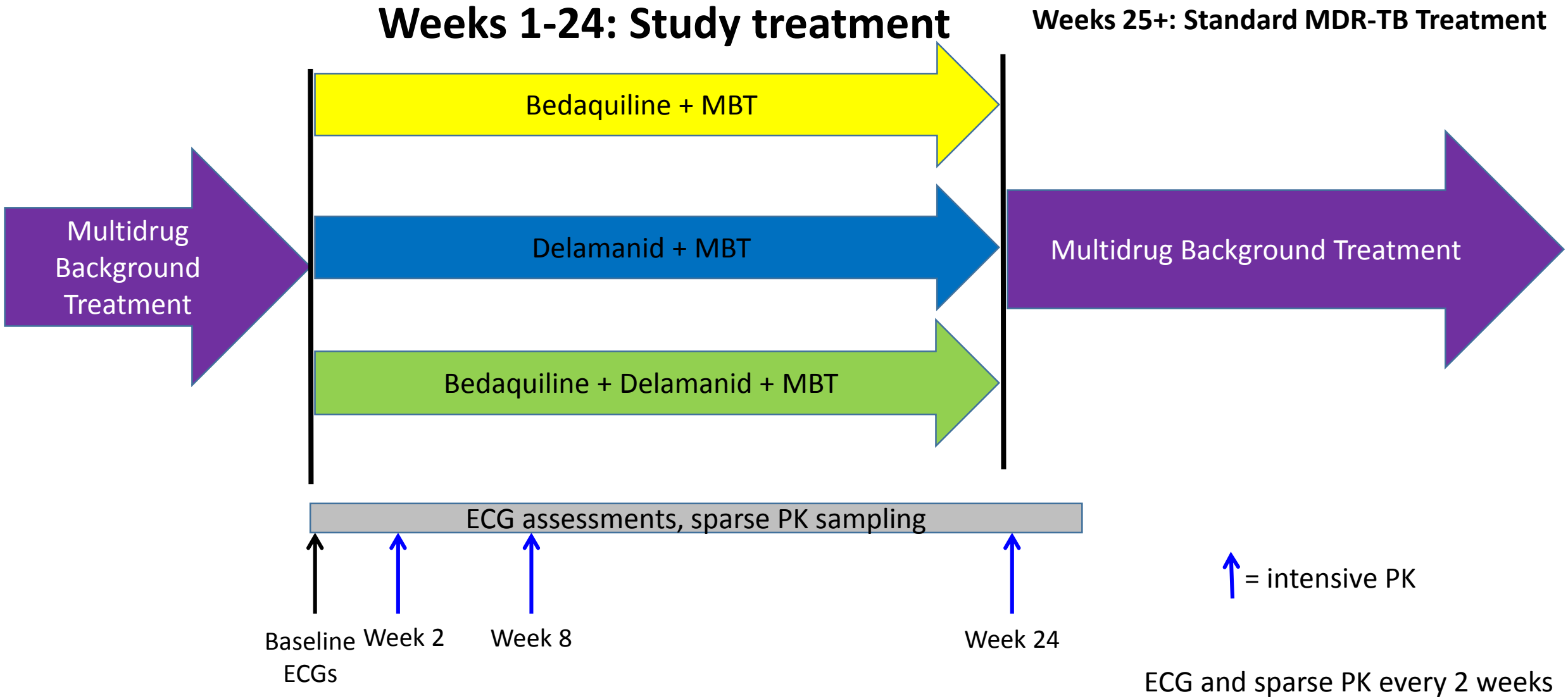
# Isoniazid: What's the right dose for patients with MDR-TB?

## *Design of A5312*




- Define **Target AUC/MIC** (based on positive control arm, max effect in experimental arms)
- Monte Carlo simulation using MIC, NAT2, AUC to **determine dose required to achieve targets.**

# ACTG A5343: The DELIBERATE Study-- Schema



# Thank you.


Roadmap for Childhood Tuberculosis: Towards Zero Deaths