# The Role of INSTIs in the Salvage Therapy

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# O Papel dos INSTIs na Terapia de resgate

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# Conflitos de Interesse (RSD)

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:

- *Pesquisa Clínica*: como médico investigador, participo de estudos patrocinados por: GSK, MSD
- *Apresentações*: como palestrante convidado, participo dos eventos de: GSK, MSD, JJ, ABBVI, BMS, Boehringer
- *Consultoria*: como membro de *advisory boards*, participo de reuniões com: GSK, MSD, JJ, ABBVI, BMS, Boehringer

Não possuo ações de quaisquer destas companhias farmacêuticas.

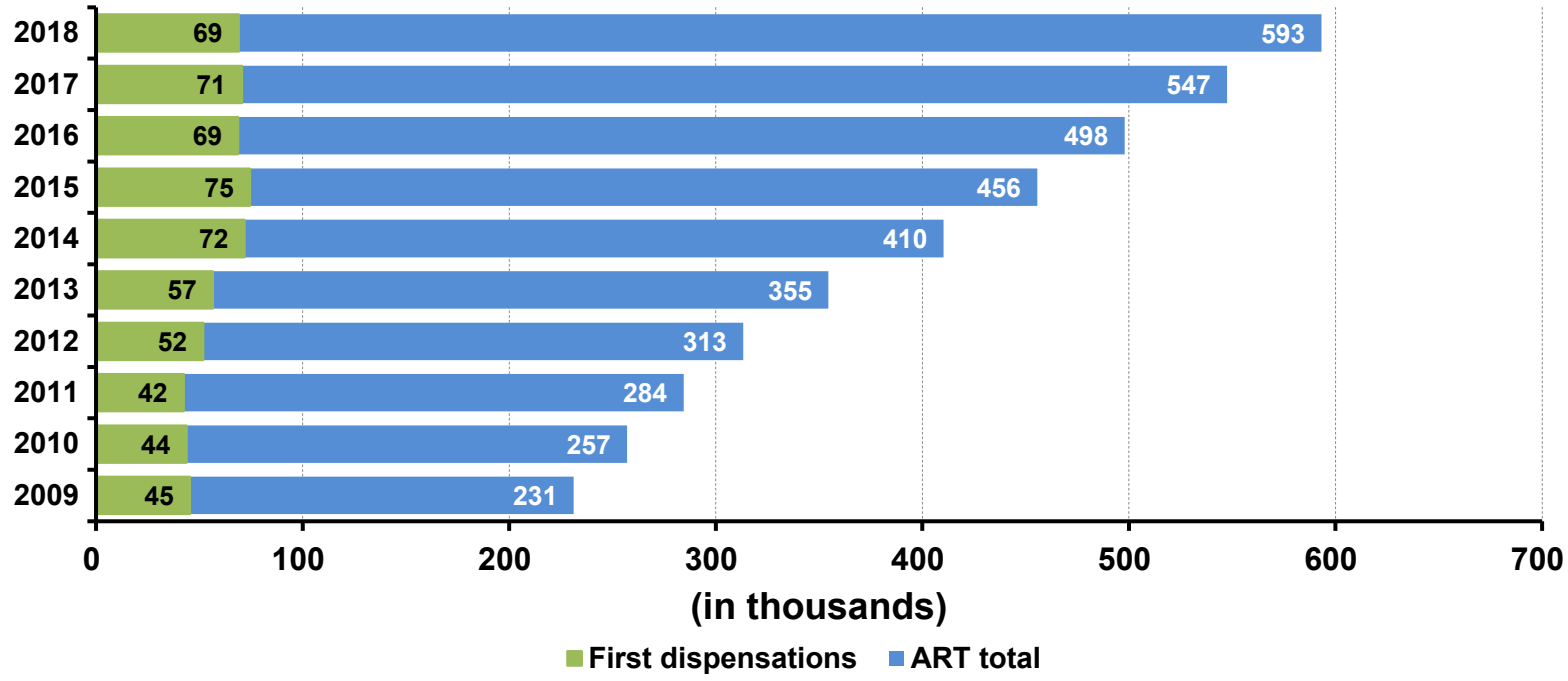
Os meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão.

- **Dados oficiais revelam que**
  - **Mais de 600 k pessoas em TARV no Brasil**
  - **No geral, cerca de 72% com CV indetectável.**
  - **Cerca de ~ 12 mil pacientes fazem genotipagem realizadas ano (2018 ->12.058; 2017 -> 11.767**
  - **31% das genotipagens com resistência a ITRN+ ITRNN+ IP**

Ministério da Saúde. Relatório de monitoramento clínico do HIV 2019. Acessado 31/08/2020 em http://www.aids.gov.br/pt-br/pub/2019/relatorio-de-monitoramento-clinico-do-hiv-2019

# ART in Brazil

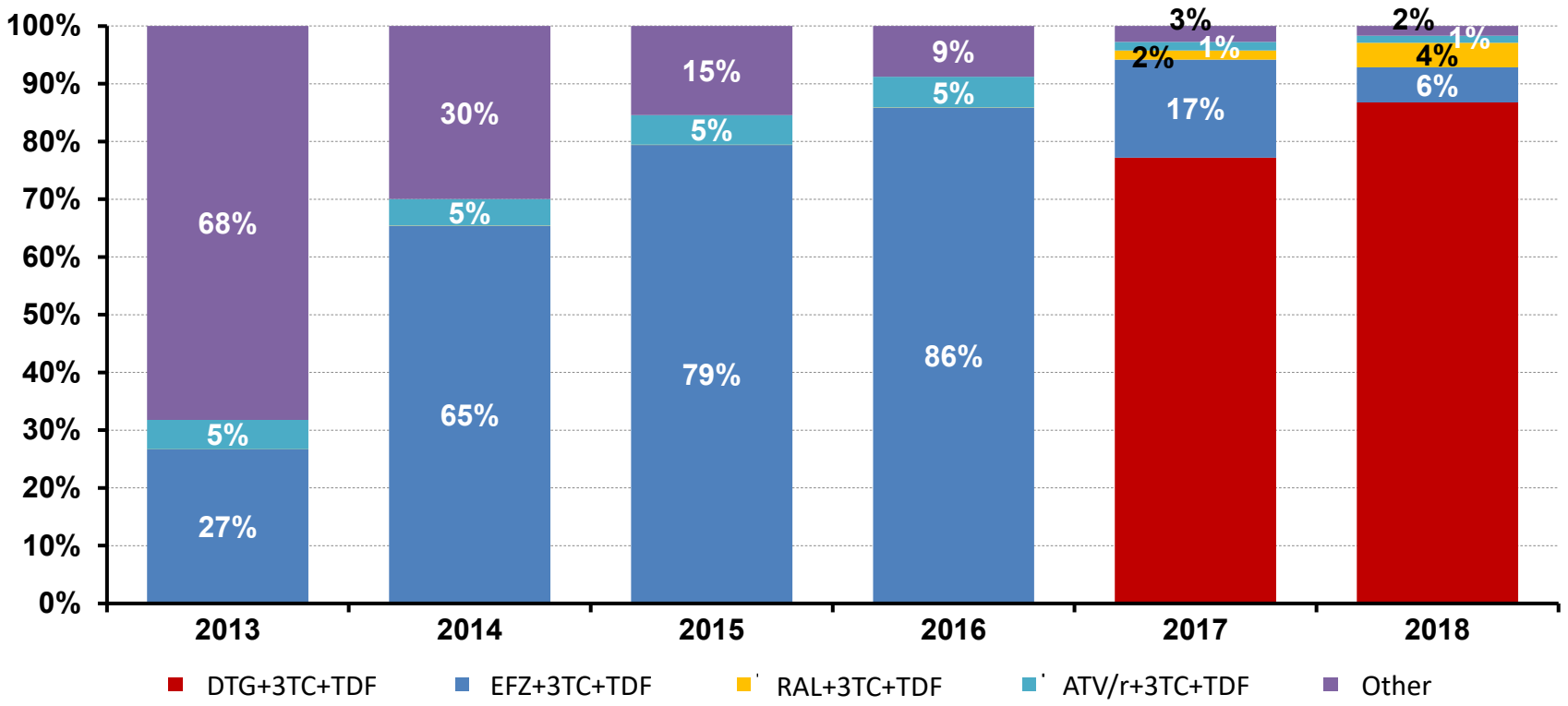
**As of as Dec 2018: 593,000 individuals on ART**






Ministério da Saúde. Relatório de monitoramento clínico do HIV 2019. Acessado 31/08/2020 em http://www.aids.gov.br/pt-br/pub/2019/relatorio-de-monitoramento-clinico-do-hiv-2019

# First Line Treatment in Brazil



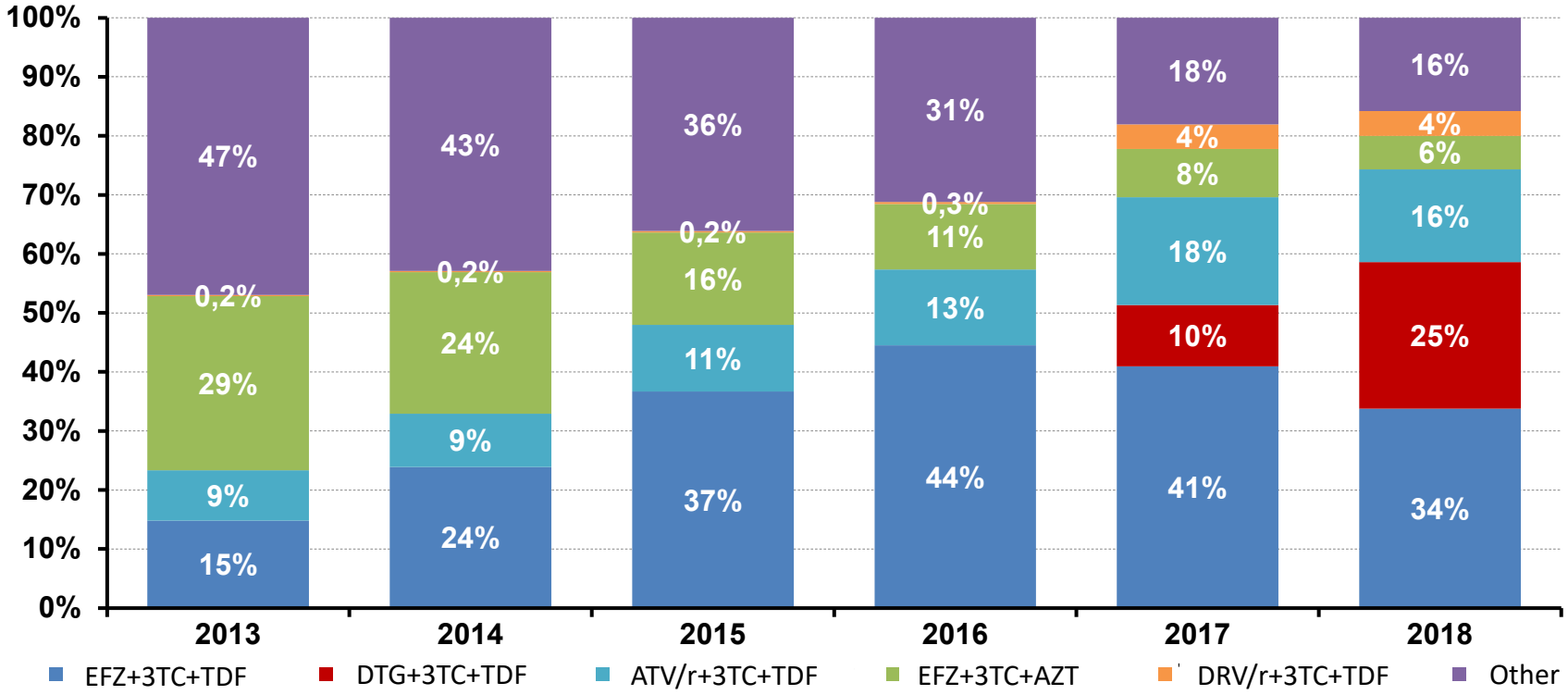

Source: Ministério da Saúde. Relatório de Monitoramento Clínico do HIV 2018 [Internet]. Available from: http://www.aids.gov.br/pt-br/pub/2018/relatorio-de-monitoramento-clinico-do-hiv-2018.

# The Selection of Resistant Mutants in the First Treatment Line

- Resistant viruses are usually not selected in the presence of b-PI + 2 or 1 NRTI (720[1] , KLEAN[2], BMS 089[3], ARTEMIS[4], CASTLE[5], GEMINI[6])
- Resistant viruses are not selected in the presence of DTG + 2 NRTIs (SPRING-1[7], SPRING-2[8], SINGLE[9], FLAMINGO[10])
- Resistant viruses are not selected in the presence of BIC/F/TAF (1489[11], 1490[12], 1878[13], 1844[14])
- All other drugs / schemes usually select resistant mutants in the first line of treatment in variable prevalence[15, 16]


1. Murphy R, et al. HIV Clin Trials. 2008;9:1-10.
2. Eron JJ Jr, et al. Lancet 2006; 368: 476-482.
3. Malan DR, et al. J Acquir Immune Defic Syndr. 2008;47:161-167.
4. Orkin, C., et al. "Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial." HIV medicine 14.1 (2013): 49-59.
5. Molina, Jean-Michel, et al. "Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1–infected patients: 96-week efficacy and safety results of the CASTLE study." Jaids Journal Of Acquired Immune Deficiency Syndromes 53.3 (2010): 323-332.
6. Walmsley SL, et al. J Acquir Immune Defic Syndr. 2009;50:367-374.
7. Stellbrink H-J, et al. AIDS 2013;27:1771–8
8. Raffi F, et al. Lancet 2013;381:735–43
9. Walmsley S, et al. N Engl J Med 2013;369:1807–18
10. Clotet B , Feinberg J, van Lunzen Jet al. . Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet2014; 383: 2222–31.
11. Gallant, Joel, et al. "Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial." The Lancet 390.10107 (2017): 2063-2072.
12. Sax, Paul E., et al. "Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial." The Lancet 390.10107 (2017): 2073-2082.
13. Daar, Eric S., et al. "Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial." The Lancet HIV 5.7 (2018): e347-e356.
14. Molina, Jean-Michel, et al. "Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial." The Lancet HIV 5.7 (2018): e357-e365.
15. Riddler SA, et al. N Engl J Med. 2008;358:2095-2106.
16. Eron JJ, et al. Lancet. 2010;375:396-407.

# ART in Brazil

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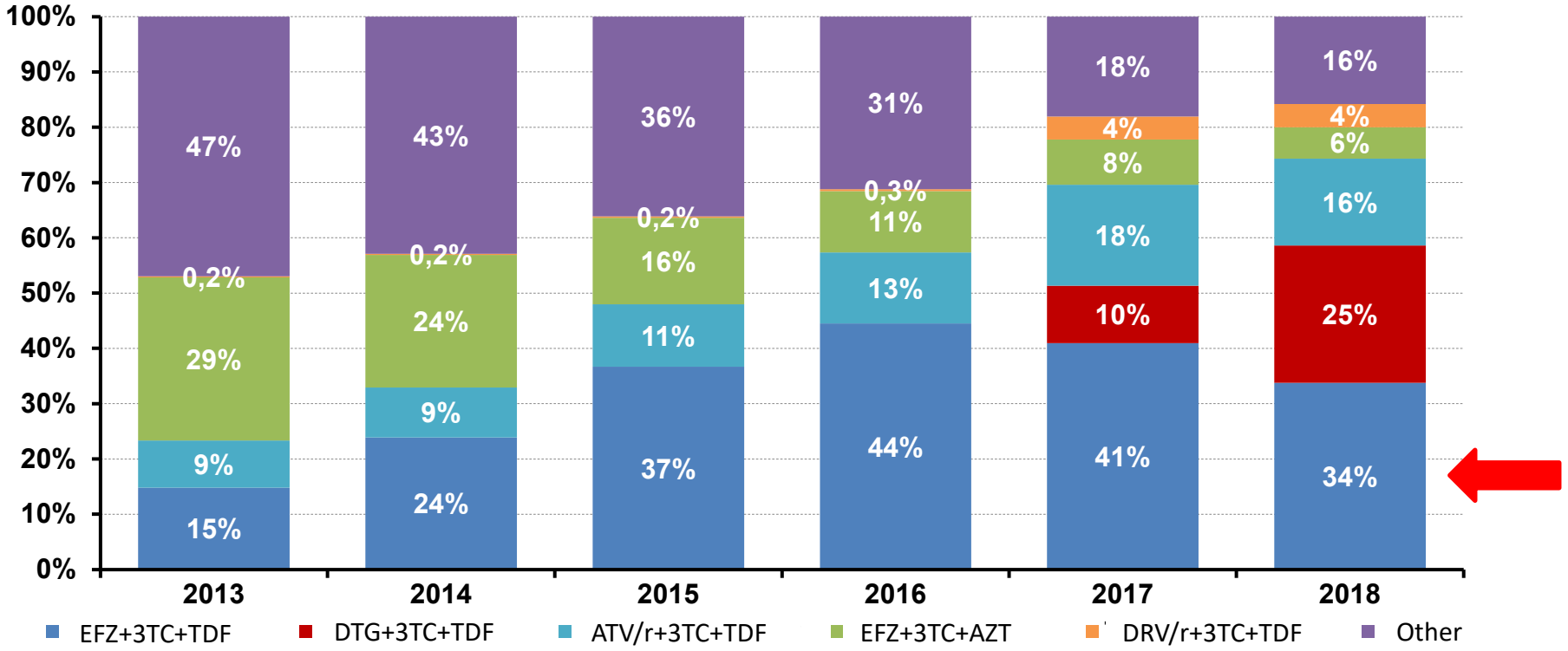
# ART in Brazil

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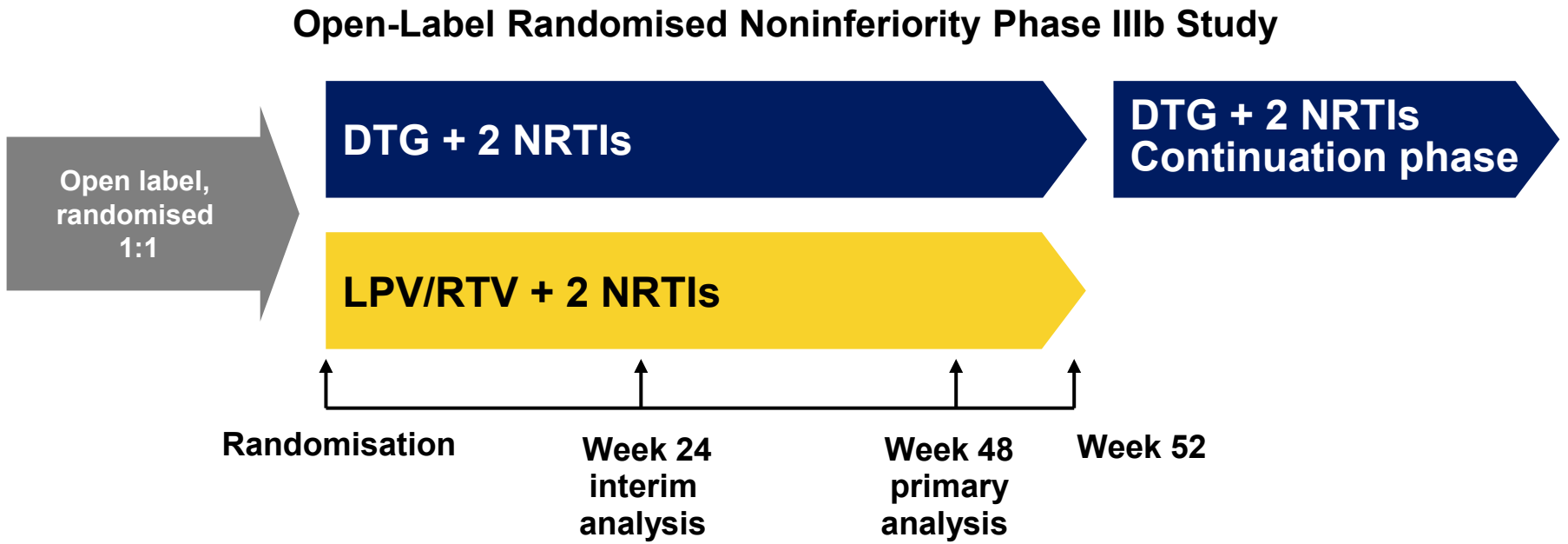
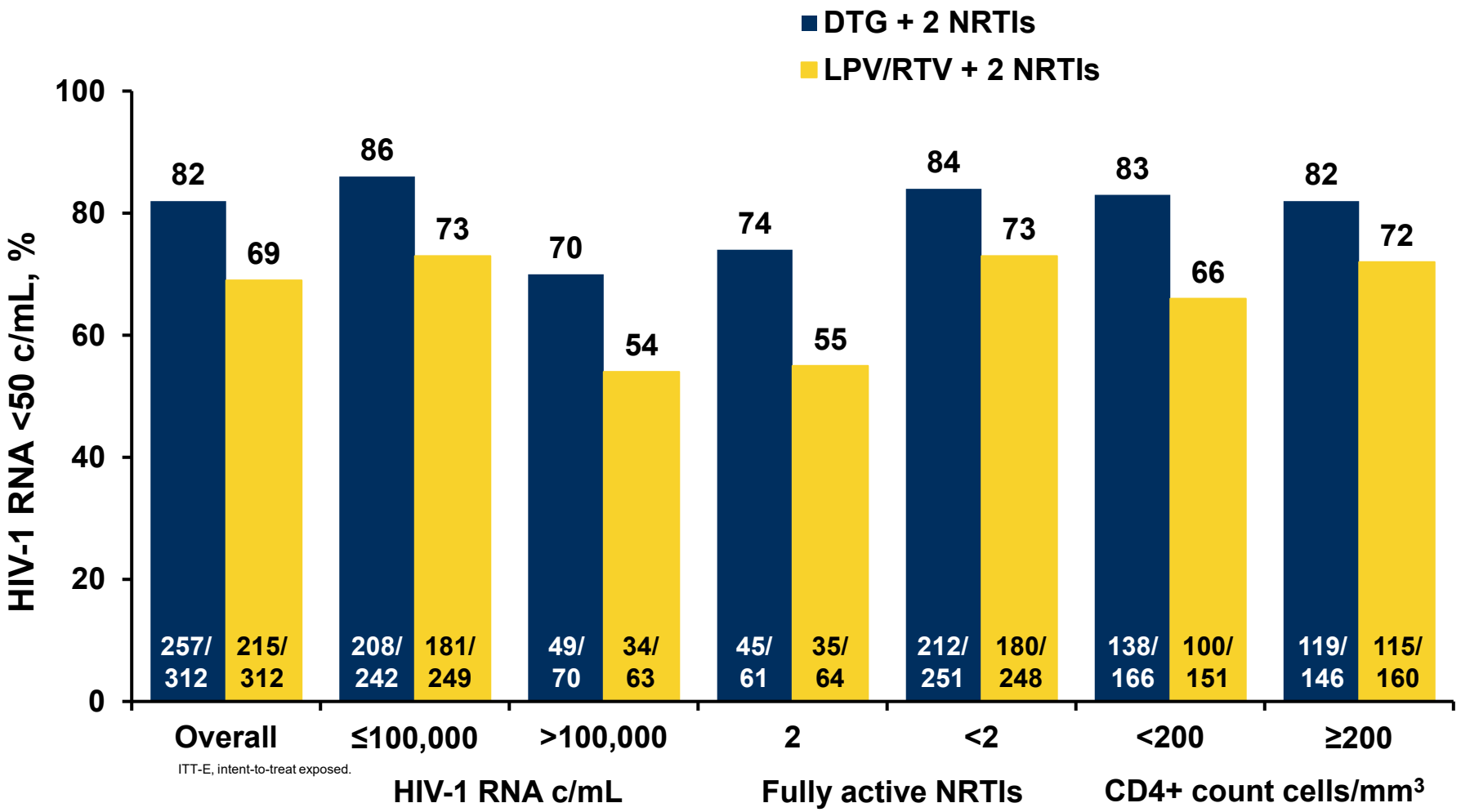
**Dawning**: first-line 2 NRTIs + NNRTI regimen for ≥6 months, failing virologically (HIV-1 RNA ≥400 c/mL on 2 occasions); no primary viral resistance to PIs or INSTIs. 312 individuals in each arm.




Aboud M, Kaplam M, Lombaard J et al. Superior effi cacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2NRTIs in second-line treatment: 48-week data from the DAWNING Study. In: 22nd International AIDS Conference. Amsterdã: 2018.

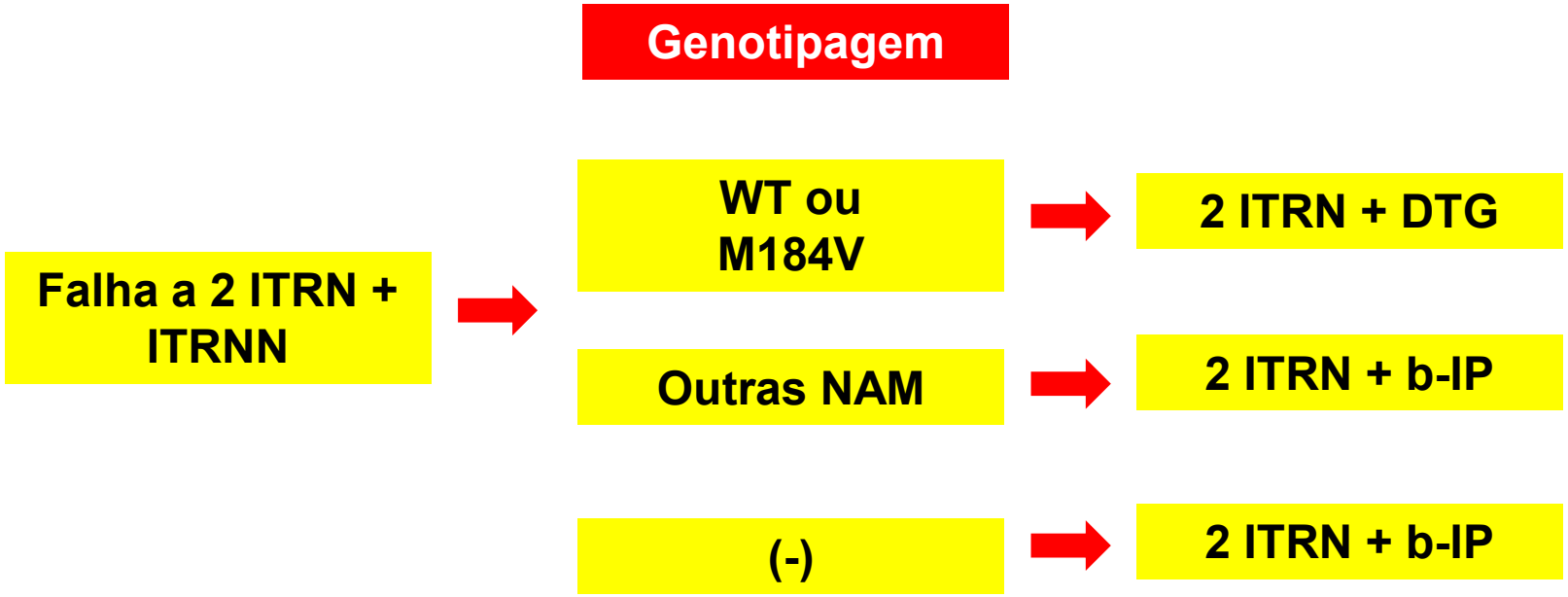
# Dawning study:
## outcomes - Subgroups at week 24



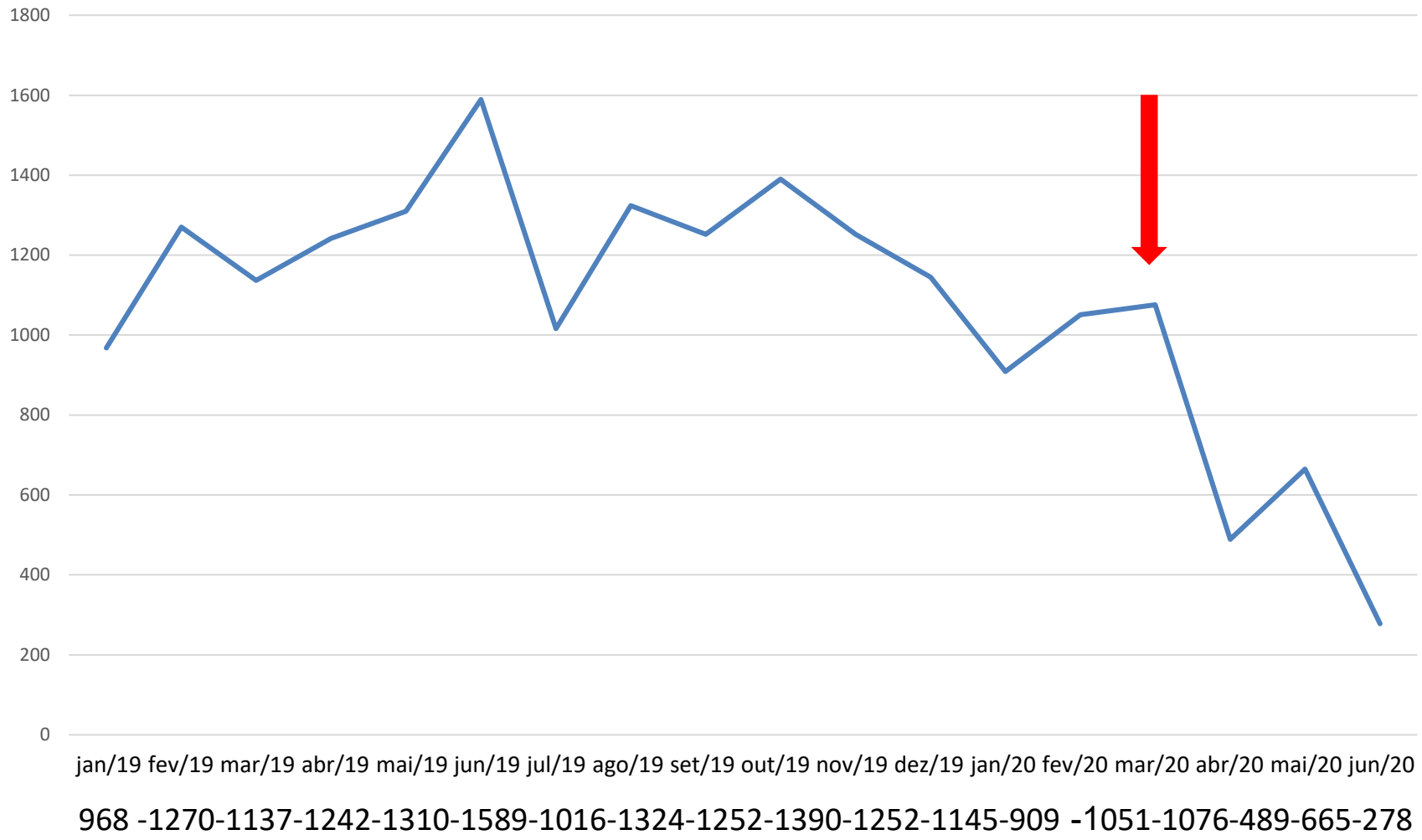

ITT-E, intent-to-treat exposed.

Aboud M, Kaplam M, Lombaard J et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2NRTIs in second-line treatment: 48-week data from the DAWNING Study. In: 22nd International AIDS Conference. Amsterdã: 2018.

# Estratégia Brasileira



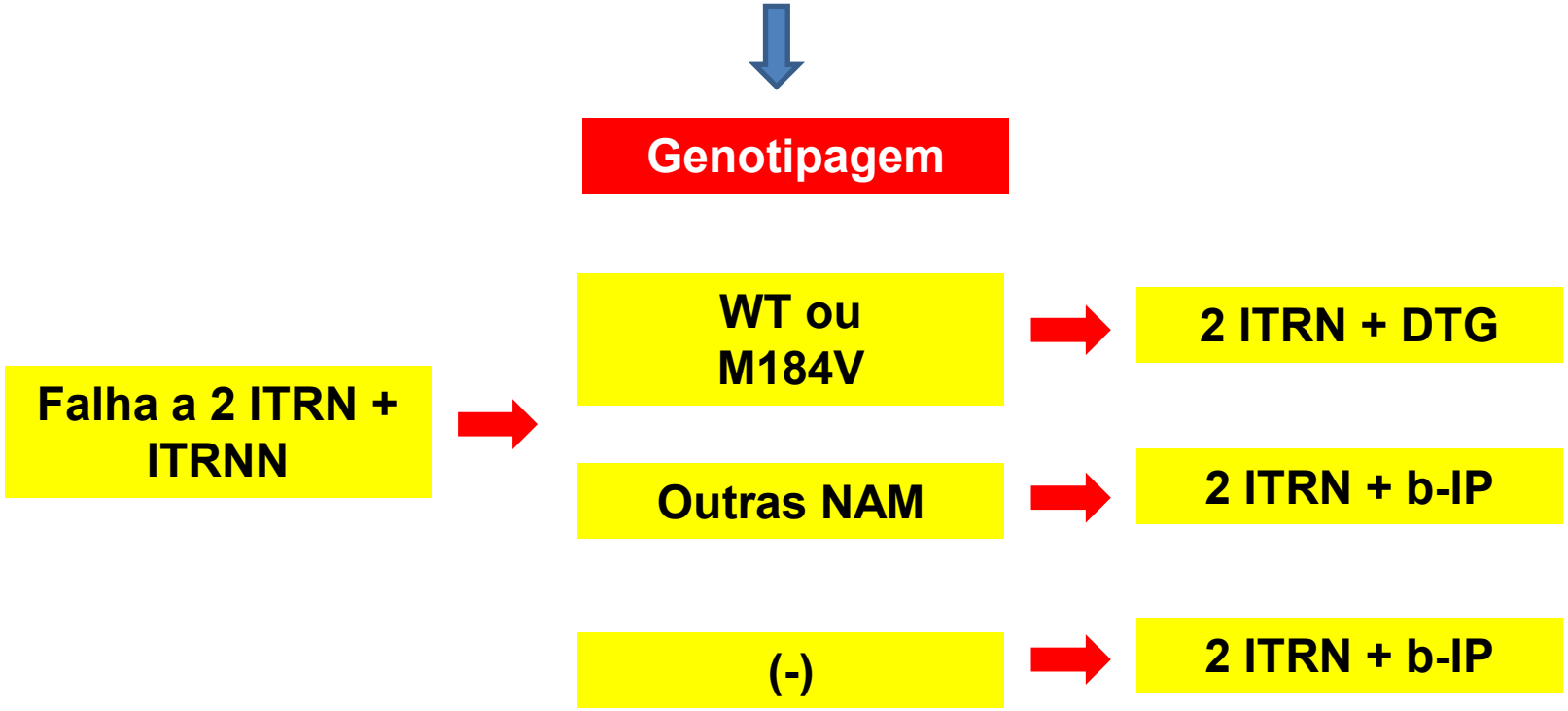
# Testes de monitoramento e a pandemia




Testes de CV com queda de 35% - L Retro/UNIFESP

Fonte Lab CdG e Lab Retrovirologia

# Estratégia Brasileira

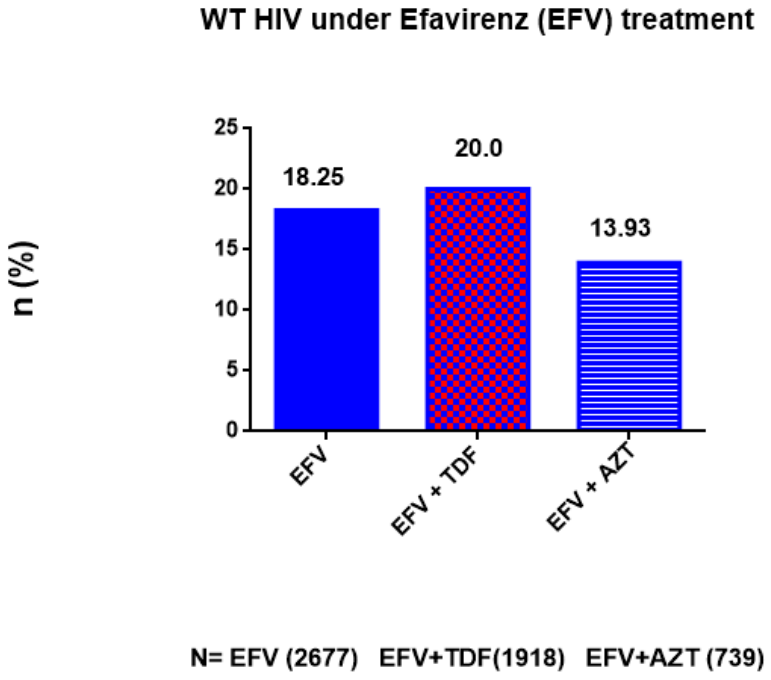


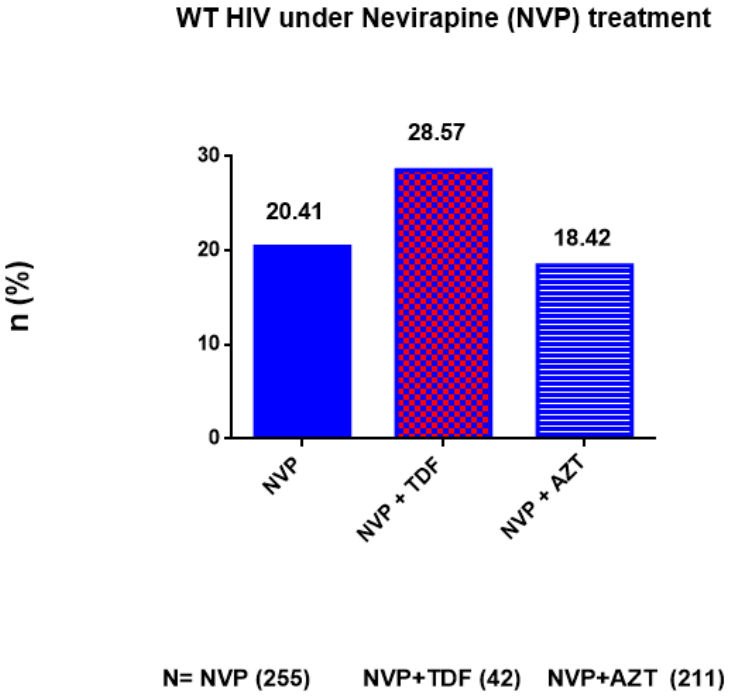
# Acquired Antiretroviral Resistance to NNRTI

- **First line failure using NNRTI**
  - **Clinical trials:**
  - **~ 50% with NNRTI RAM (K103N)**
  - **~ 25% with M184V (Always with K103N)**
  - **~ 50% with WT**
  - **No other NAMs**

Riddler SA, et al. N Engl J Med. 2008;358:2095-2106.
Daar E, et al. Ann Intern Med. 2011;154:445-456.

# Prevalence of Individuals with WT HIV Strains upon First Line Treatment Failure with NNRTIs (2017-18)

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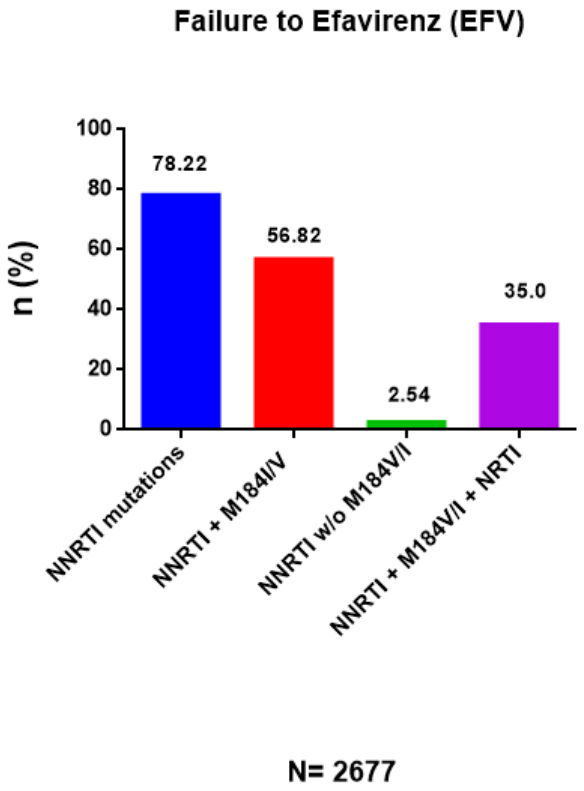
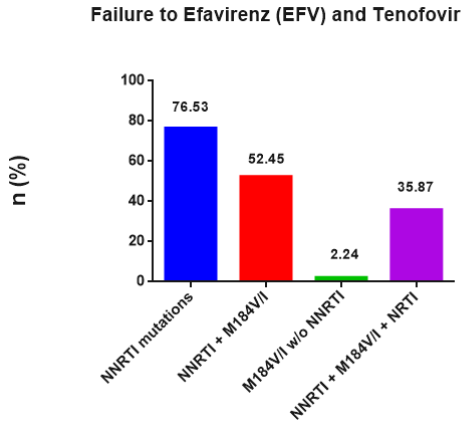
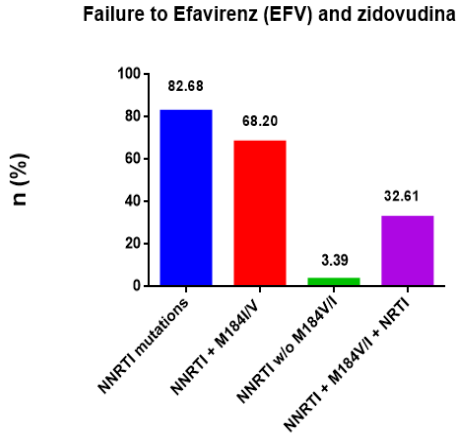
# Prevalence of Class Mutation to First Line Treatment Failure with Efavirenz (2017-18)




N= 2677




N=1918




N=739

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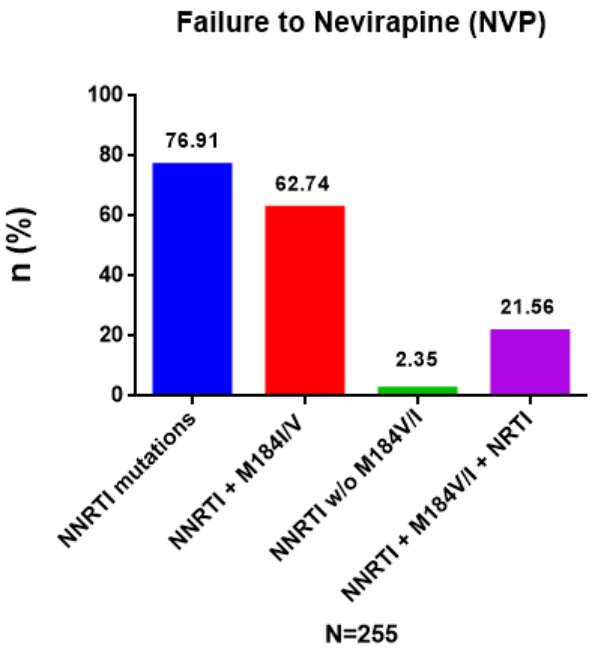
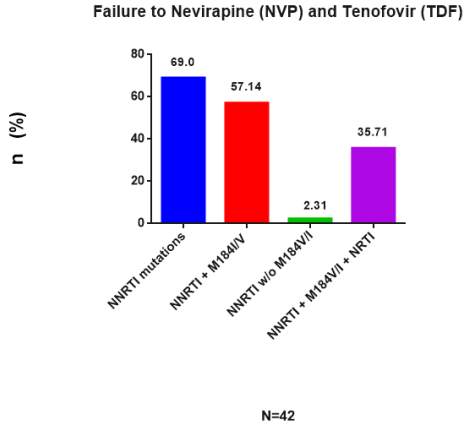
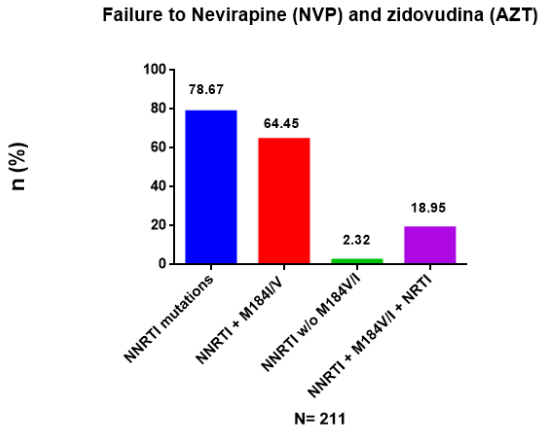
# Prevalence of Class Mutation to First Line Treatment Failure with Nevirapine (2017-18)

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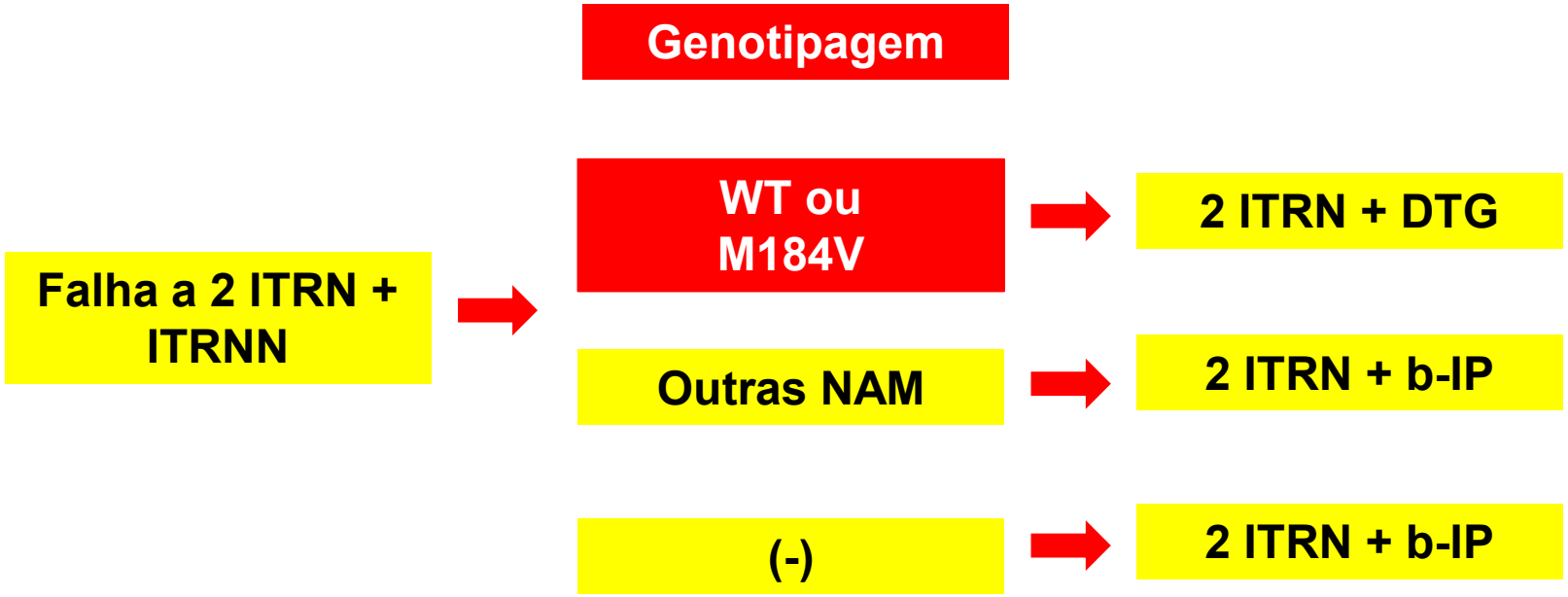
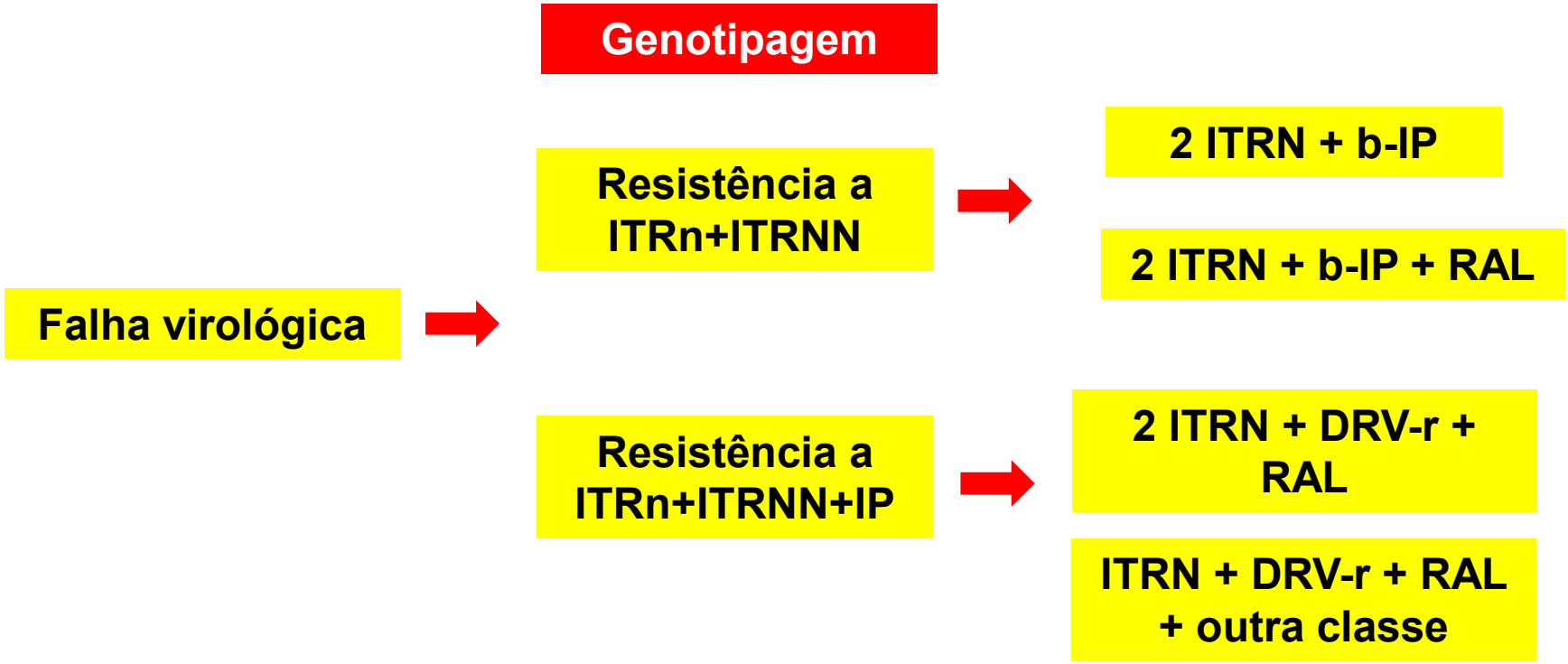
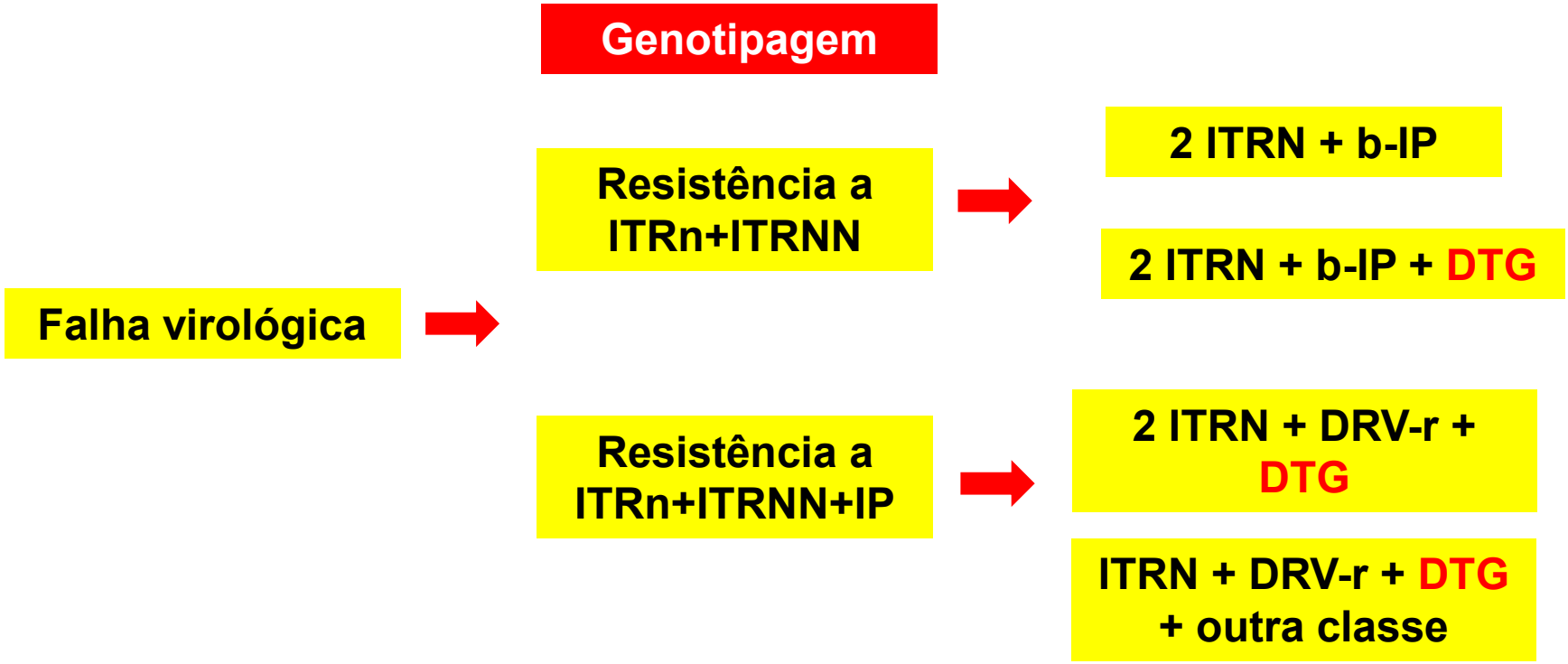
# Estratégia Brasileira



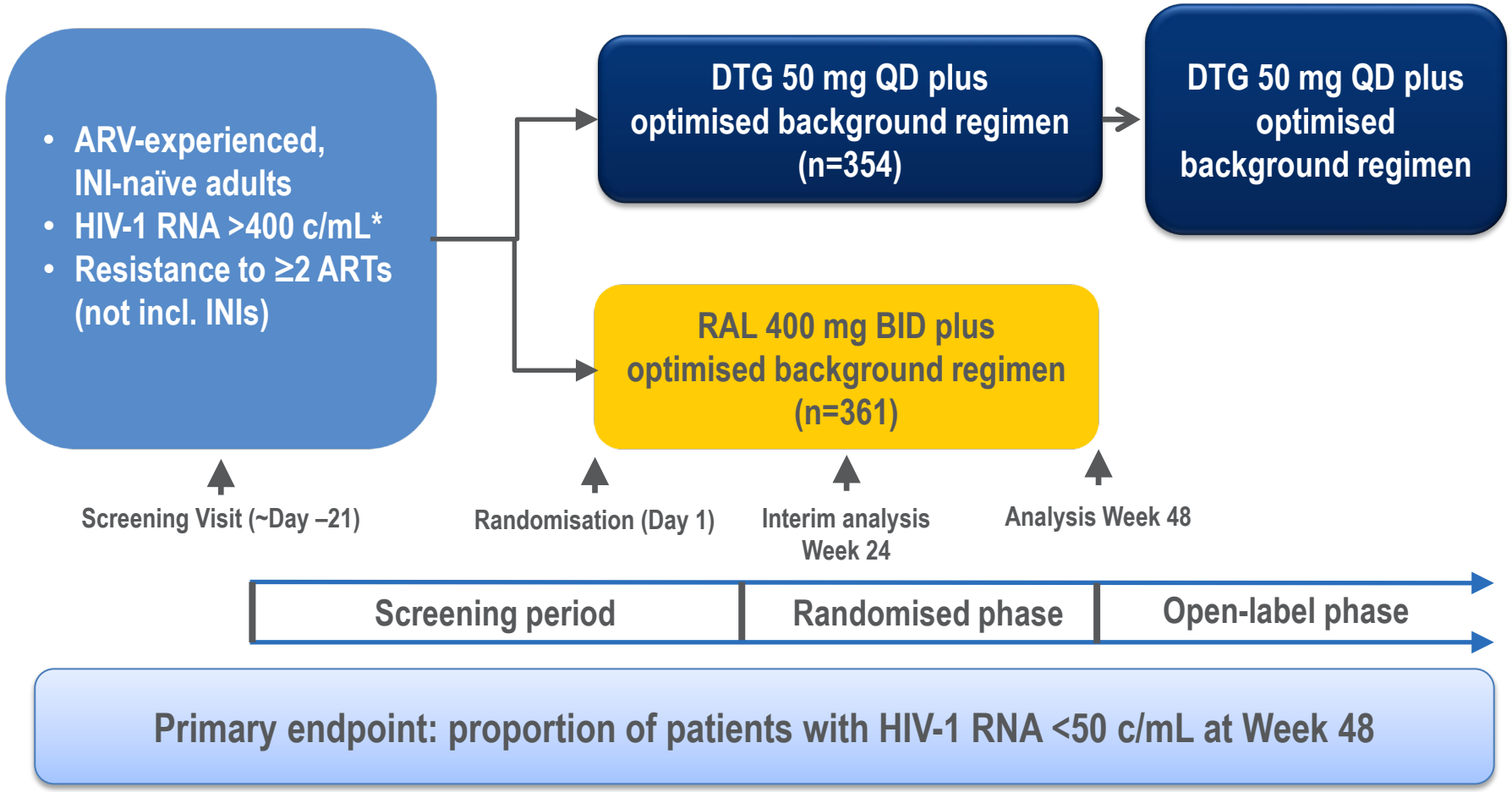
# Estratégia Brasileira até 2017



# Estratégia Brasileira desde janeiro 2017



# SAILING: STUDY DESIGN



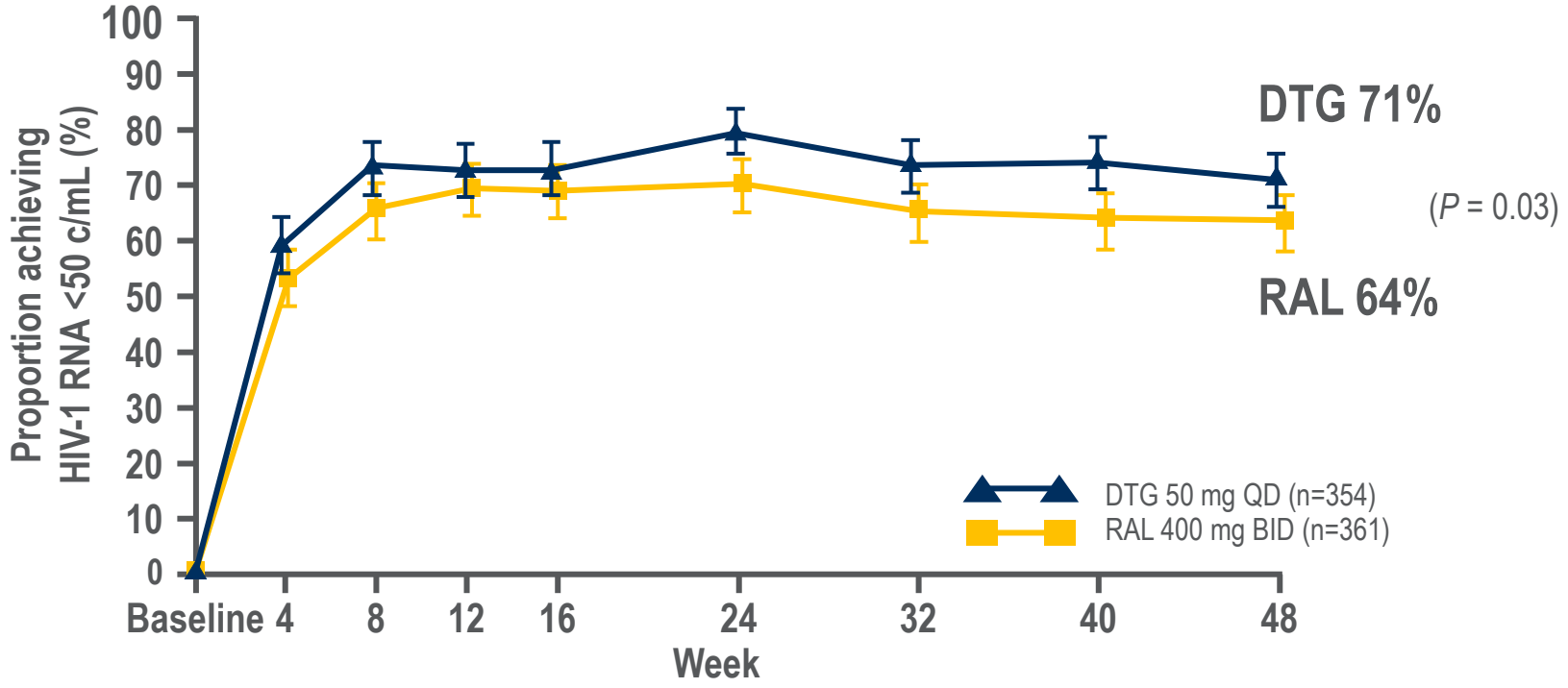

Cahn P, et al. *Lancet* 2013;382(9893):700-708

# BASELINE CHARACTERISTICS

| | DTG 50 mg QD (N=354) | RAL 400 mg BID (N=361) |
|---|---|---|
| **Age, median (years)** | 42 | 43 |
| **Gender, female** | 30% | 34% |
| **Race** | | |
| White | 49% | 48% |
| African American or African heritage | 40% | 44% |
| **HIV-1 RNA, median ($log_{10}$ c/mL)** | 4.17 | 4.21 |
| >50,000 c/mL | 30% | 30% |
| **CD4+ count, median (cells/$mm^3$)** | 205 | 193 |
| **HBV coinfection** | 5% | 4% |
| **HCV coinfection** | 9% | 13% |
| **Duration prior ART, median (months)** | 80 | 72 |
| **≥3 class resistance** | 47% | 51% |
| **Most common background regimens, n (%)** | | |
| DRV/r, TDF | 62 (18) | 73 (20) |
| LPV/r, TDF | 40 (11) | 40 (11) |
| DRV/r, ETR | 33 (9) | 40 (11) |
| LPV/r | 36 (10) | 35 (10) |
| ATV/r, TDF | 37 (10) | 33 (9) |
| DRV/r, MVC | 23 (6) | 19 (5) |

Cahn P, et al. Lancet 2013;382:700–8

# SAILING

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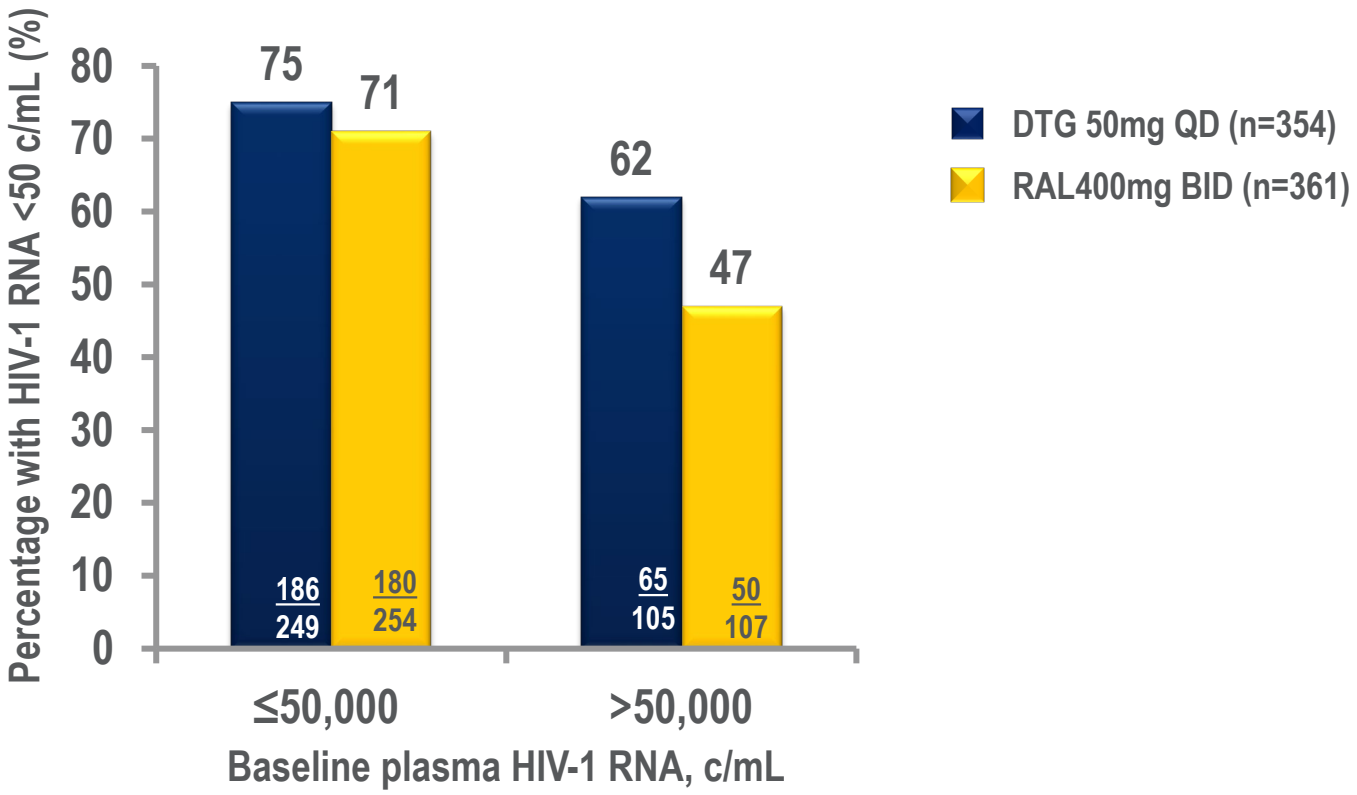
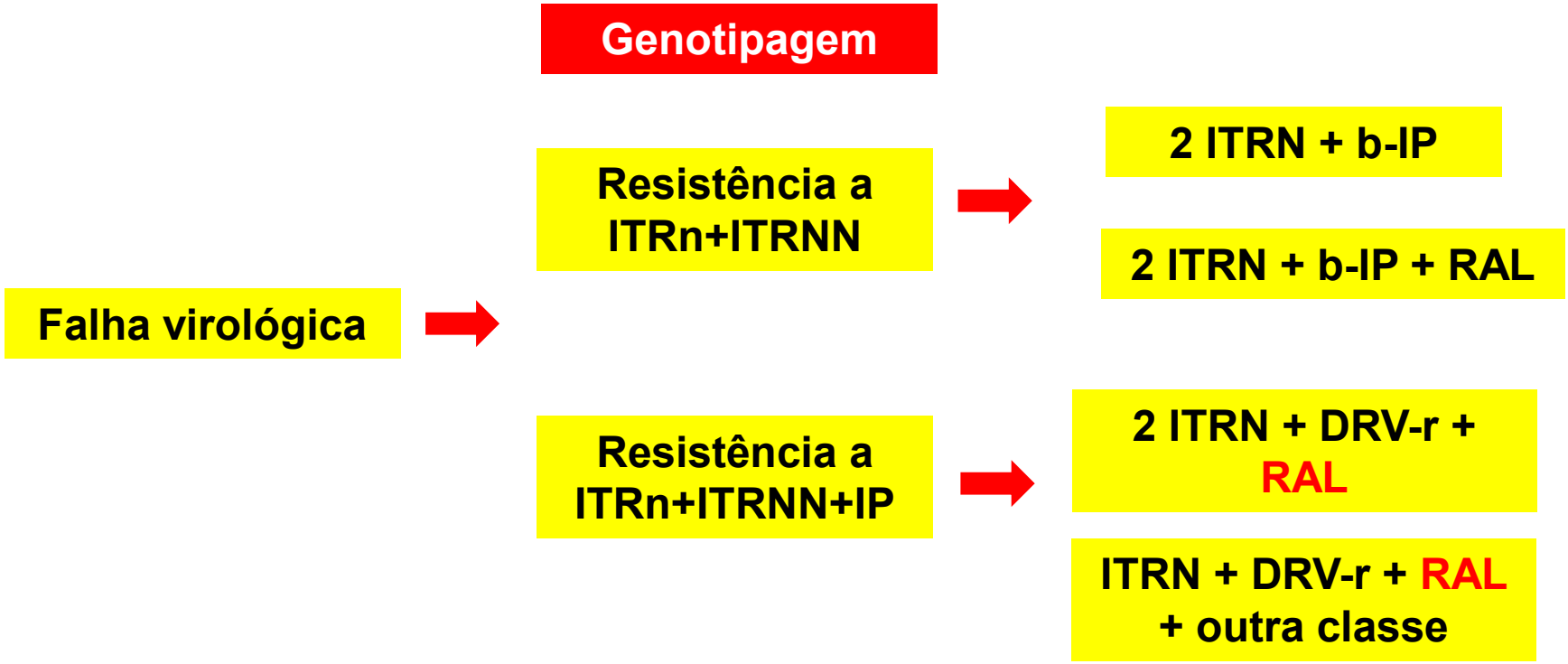
# SAILING



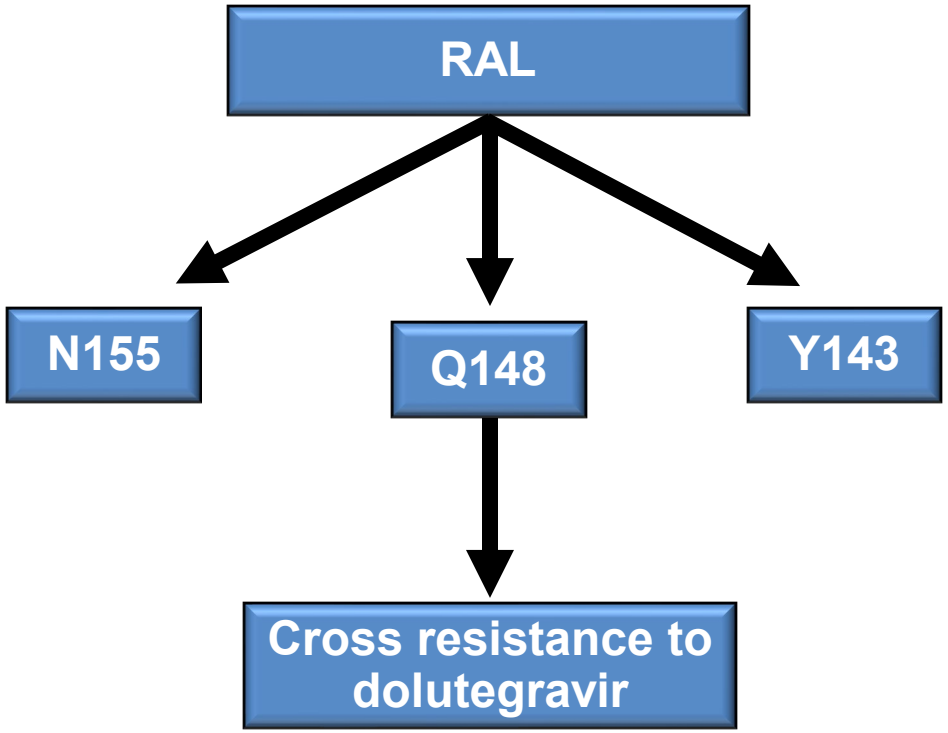

- 30% of patients had baseline viral load >50,000 copies/mL

Cahn P, et al. *Lancet* 2013;382(9893):700-708

# Estratégia Brasileira até 2017



# Raltegravir Mutational Pathways





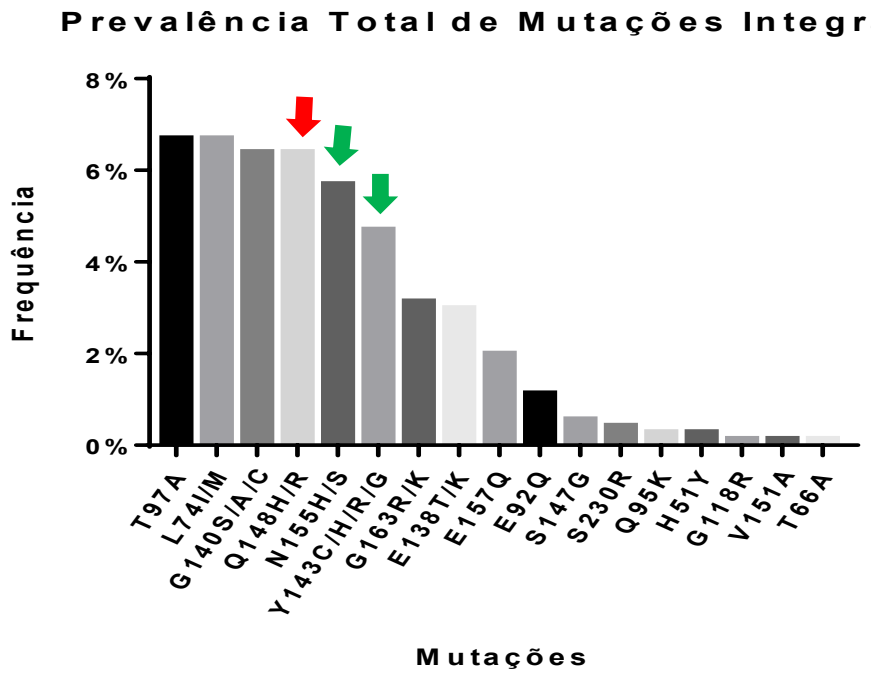

Fransen S, et al. Antimicrob Agents Chemother. 2009;53:4522-4544.
Hatano H, et al J Acquir Immune Defic Syndr. 2010;54:389-393.

# Susceptibility of Raltegravir-Resistant HIV-1 Isolates to Dolutegravir

| Genotype | Dolutegravir | | Raltegravir | | N |
|---|---|---|---|---|---|
| | Median FC | Range FC | Median FC | Range FC | |
| N155H | 1.37 | 1.22-1.45 | 19.0 | 14.0-36.0 | 5 |
| G140S, Q148H | 3.75 | 2.05-15.0 | > 87 | 58 - > 87 | 7 |
| G140S, Q148R | 13.3 | 7.57-19.0 | > 87 | > 87 - > 87 | 2 |
| T97A, Y143R | 1.05 | 1.04-1.06 | > 81 | > 81 - > 81 | 2 |

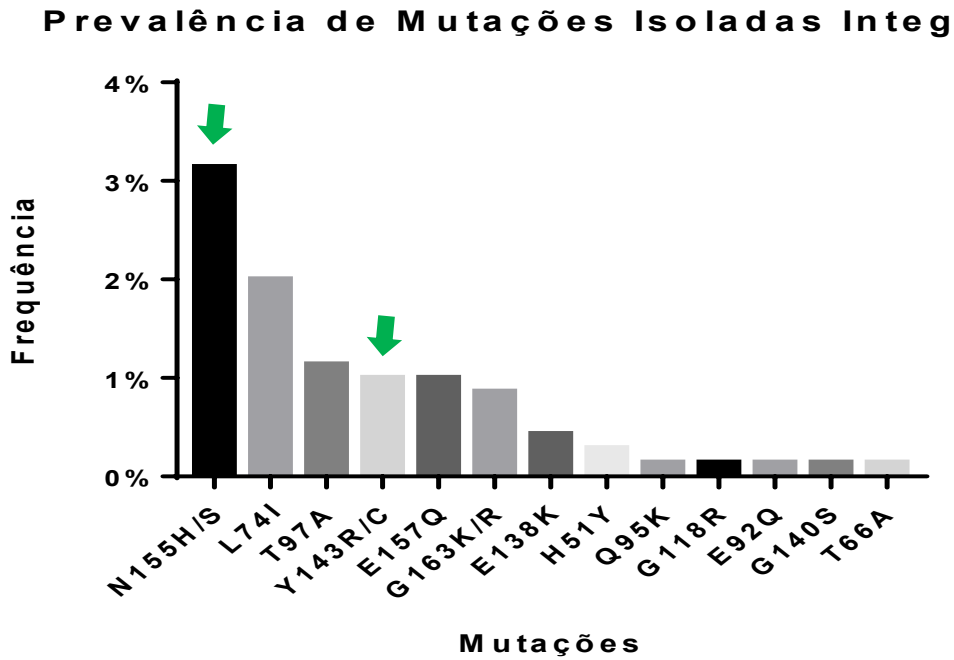
Underwood M, et al. J Acquir Immune Defic Syndr. 2012 Nov 1;61(3):297-301

## 182/701 (26%) pacientes com mutações na integrasse na falha a resgate com RAL: Jan 2017 a Dez 2018



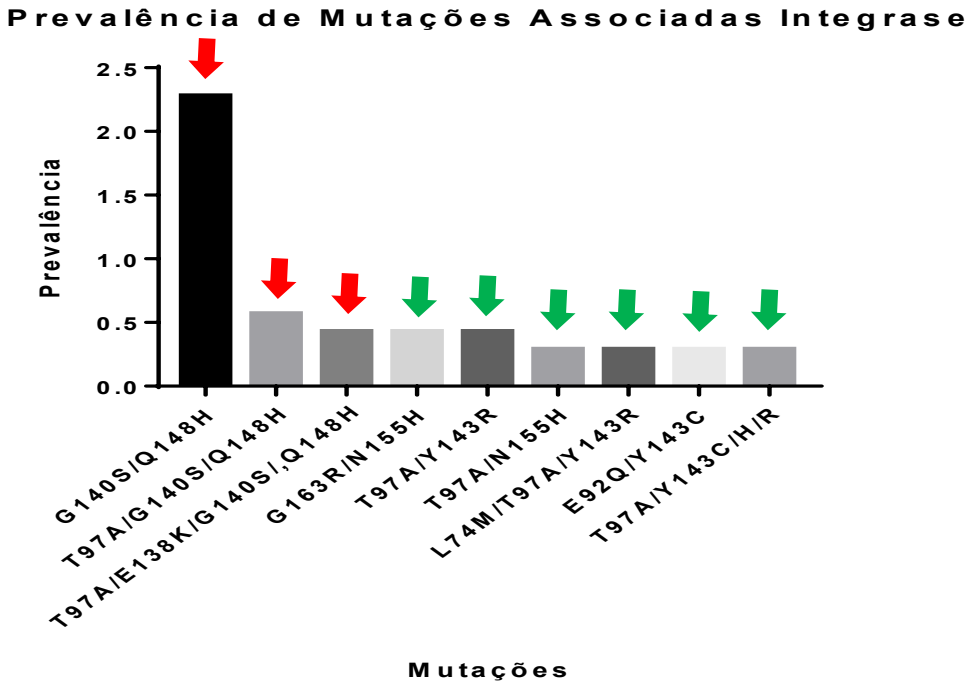

Nassar I et al, dados não publicados

**182/701 (26%) pacientes com mutações na integrasse na falha precoce do resgate com RAL (uma única mutação)**



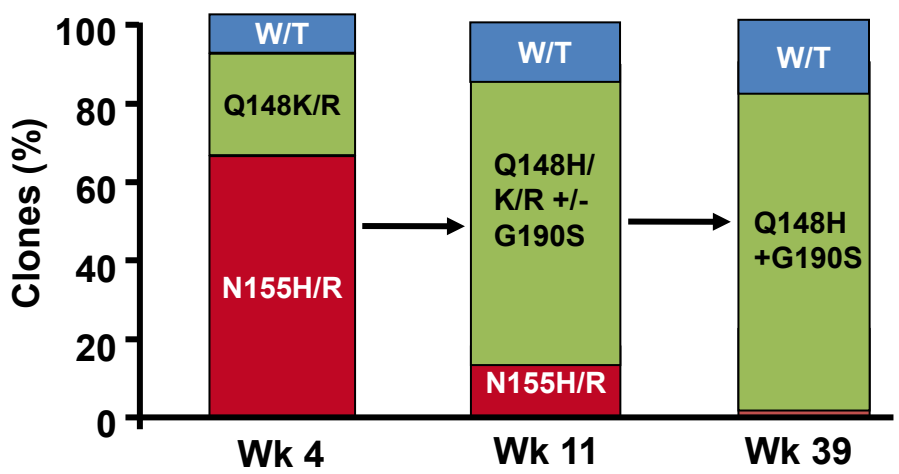

Nassar I et al, dados não publicados

**182/701 (26%) pacientes com mutações na integrasse na falha tardia do resgate com RAL (mais de uma mutação)**




Nassar I et al, dados não publicados

# Evolution of Integrase Resistance With Increased Time After Virologic Failure

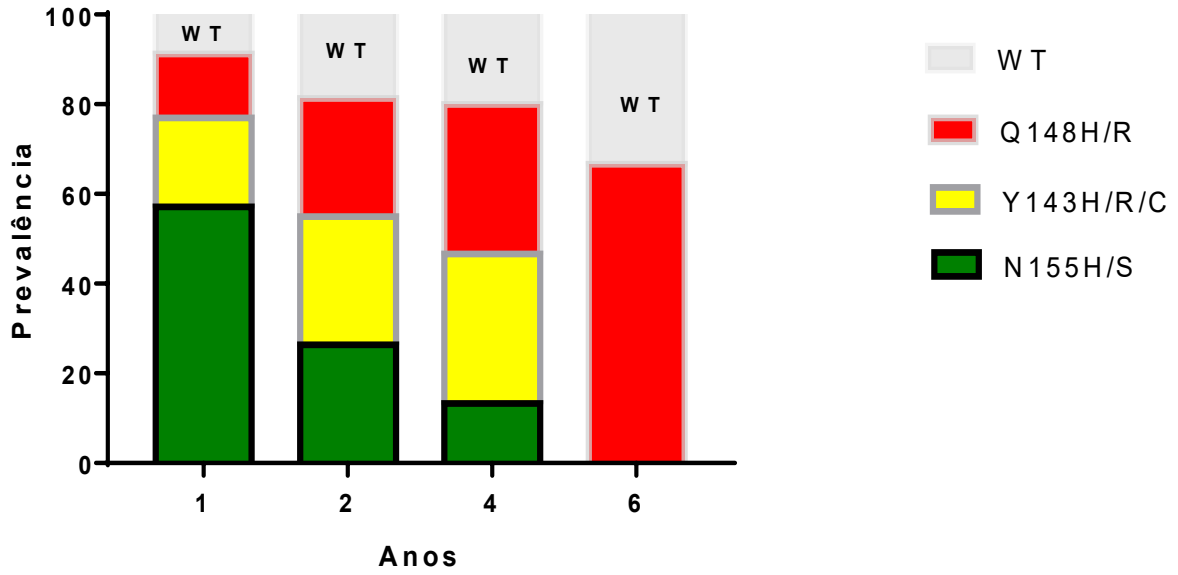



- Q148H/K/R or Y143R/H/C —high-level phenotypic resistance
  - Change in IC50 > 100-fold
- N155H — lower-level phenotypic resistance
  - Change in IC50 < 50-fold

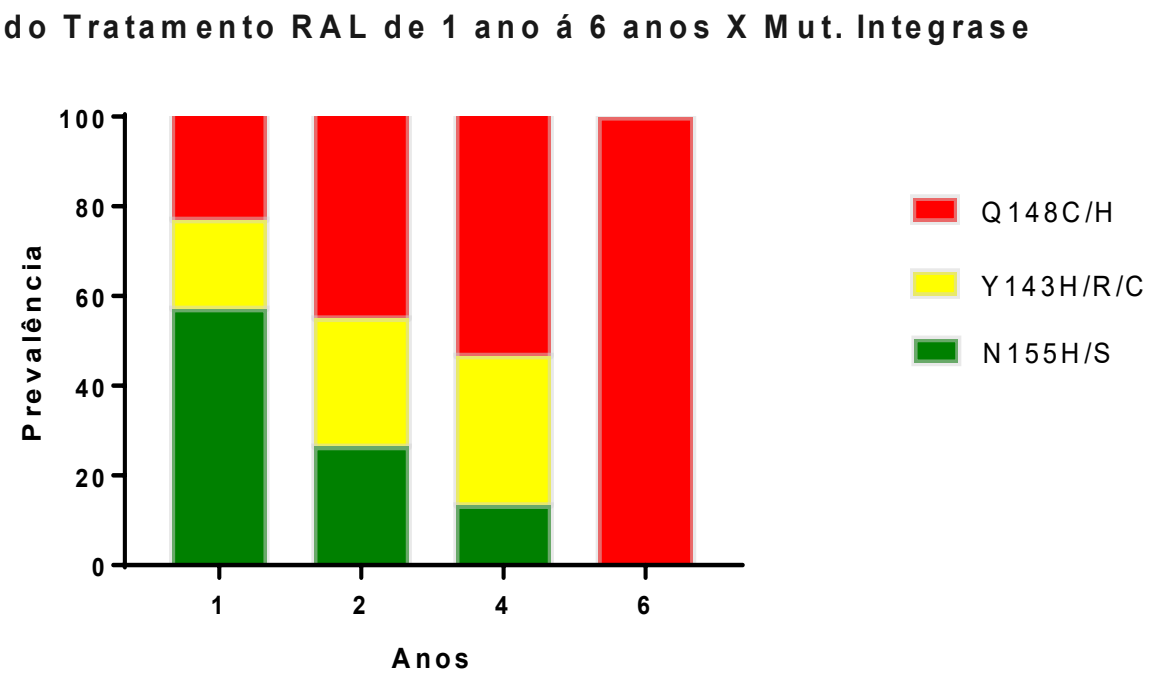

Fransen S, et al. Antimicrob Agents Chemother. 2009;53:4522-4544.

Hatano H, et al J Acquir Immune Defic Syndr. 2010;54:389-393.

## Duração do Tratamento RAL de 1 ano á 6 anos X Mut. Integrase




Nassar I, 2020, Tese de mestrado, UNIFESP

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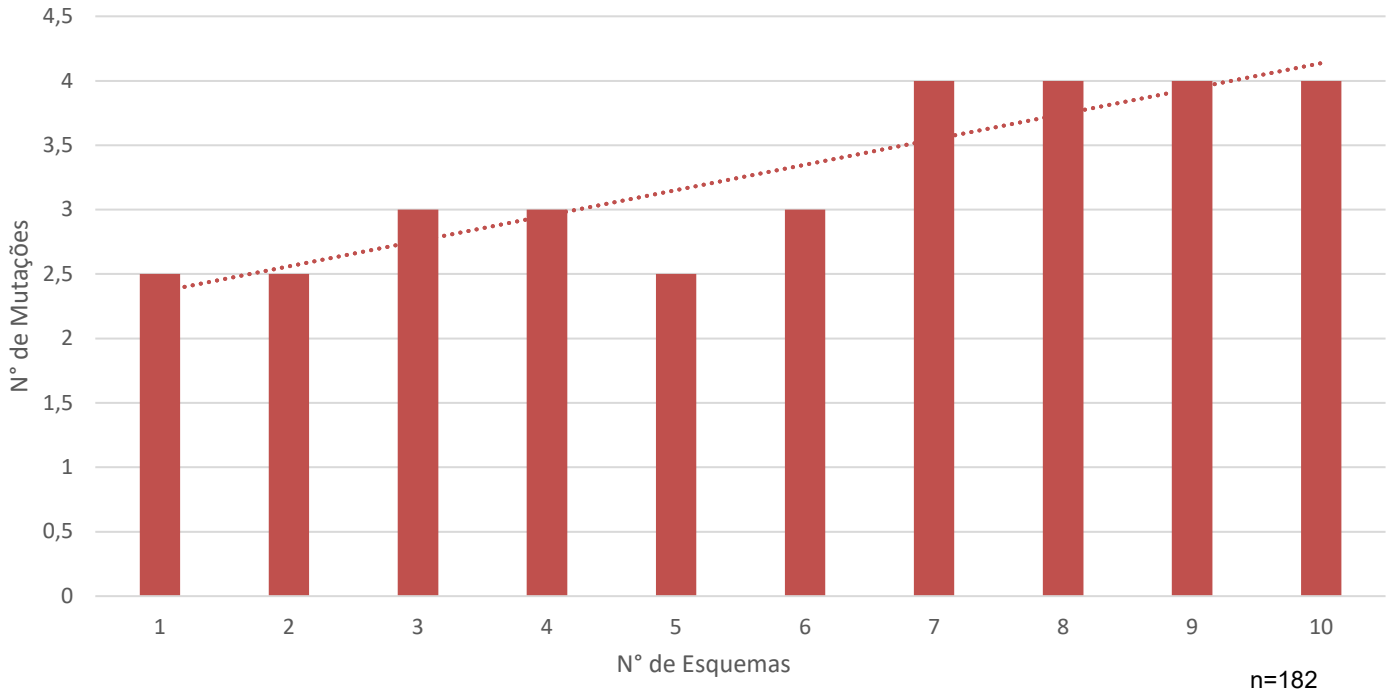
# Número de mutações acumuladas na integrasse de acordo com o número de esquemas ARV usados




Nassar I, 2020, Tese de mestrado, UNIFESP

# Dolutegravir em pacientes infectados experimentados e com resistência ao raltegravir e/ou ao elvitegravir: VIKING-3

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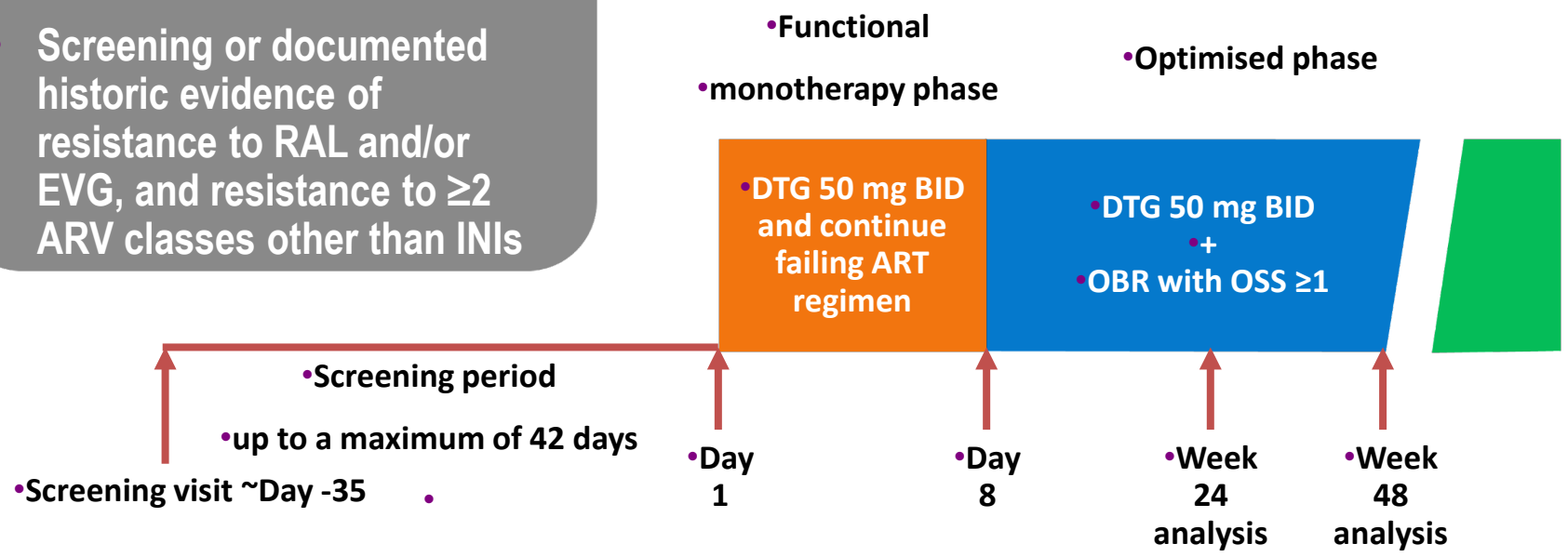
CASTAGNA, A. et al. Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir- Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study J Infect Dis, 2014. Epub.

# VIKING-3: study design (N=183)

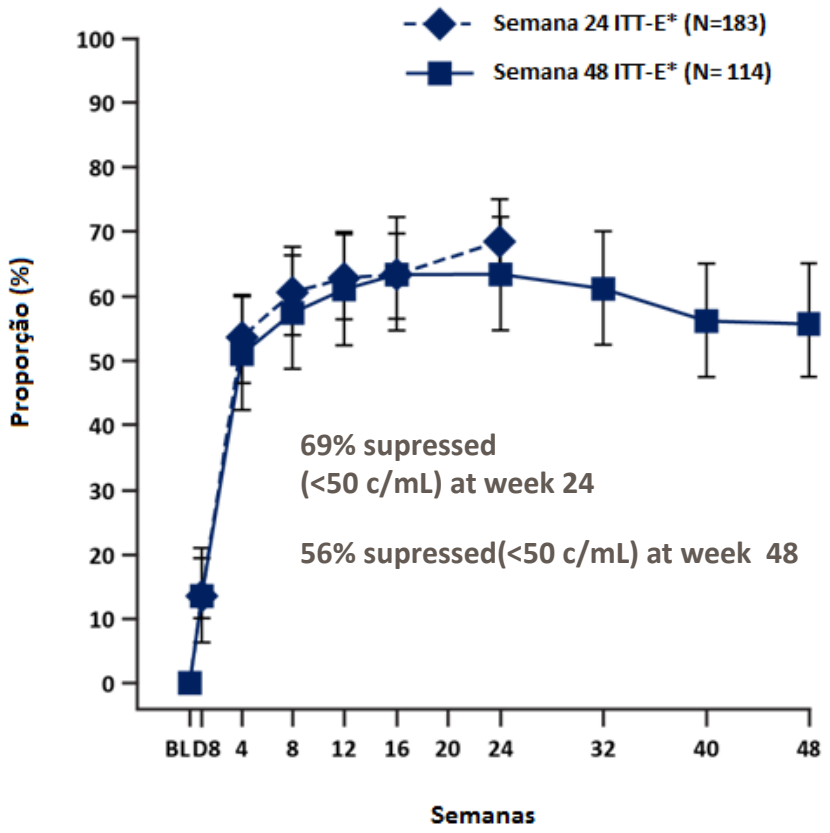
- Main eligibility criteria:
  - HIV-1 RNA ≥500 c/mL
  - Screening or documented historic evidence of resistance to RAL and/or EVG, and resistance to ≥2 ARV classes other than INIs




Castagna A, et al. J Infect Dis 2014;210:354–62

# VL < 50 c/mL (Snapshot)

| Results | DTG 50 mg 2x dia | |
|---|---|---|
| | Semana 24 ITT-E (N=183) | Semana 48 ITT-E (N=114) |
| **Virologic supression** | 126 (69%) | 64 (56%) |
| **No response** | 50 (27%) | 44 (39%) |
| **No VL data** | 7 (4%) | 6 (5%) |
| **Descontinuation related to AE or death** | 5 (3%) | 5 (4%) |
| **Descontinuation for other reazons** | 2 (1%) | 1 (<1%) |




*Intention-to-treat Exposed

# Week 24 and Week 48 Response by Baseline Integrase Mutations*

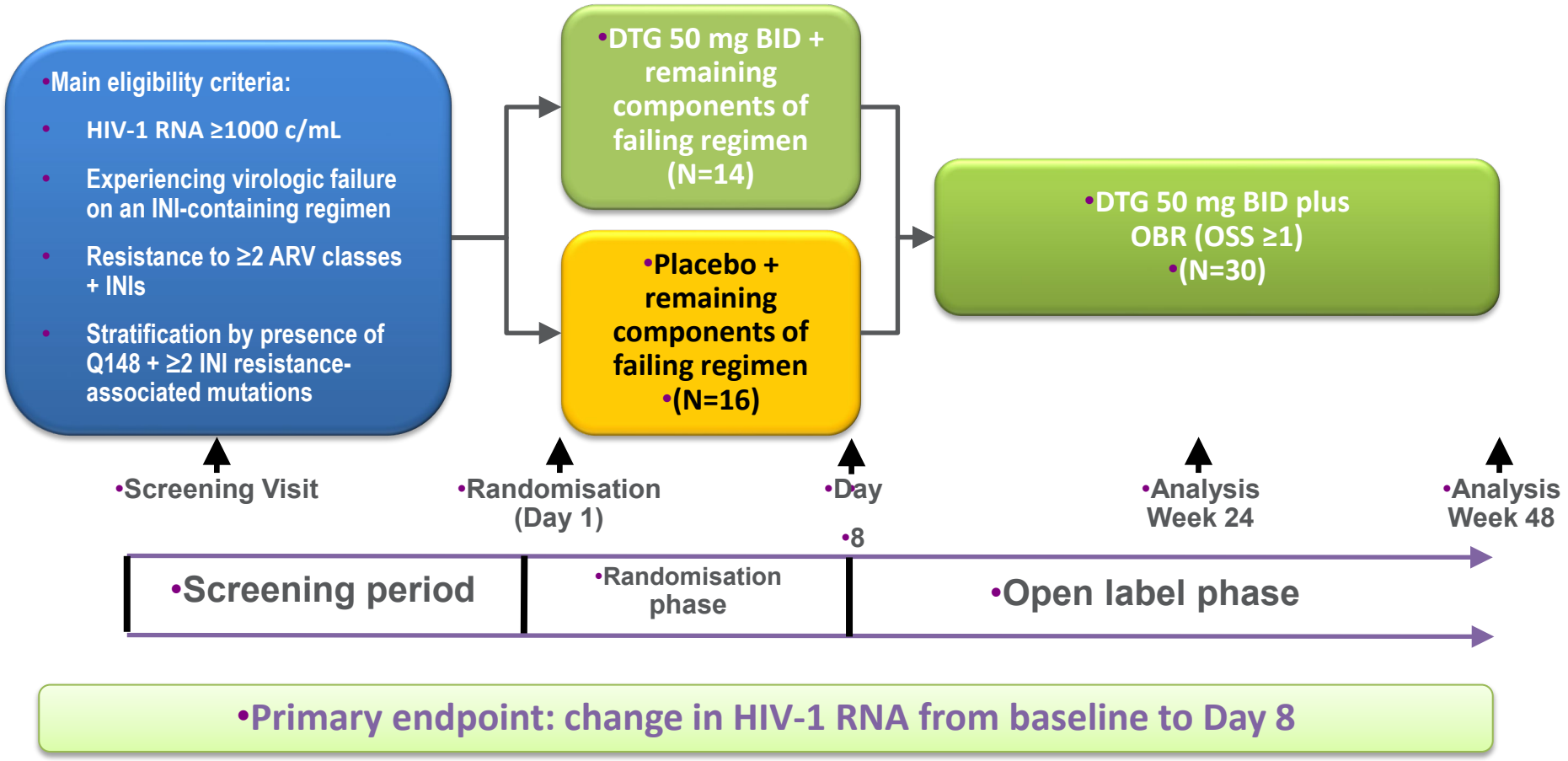
| Derived IN mutation group at BL | N | HIV-1 RNA <50 c/mL at Week 24,[1] % | HIV-1 RNA <50 c/mL at Week 48,[2] % |
|---|---|---|---|
| Total | 183 | 69 | 63 |
| No Q148 | 126 | 79 | 71 |
| Q148 + 1 secondary mutation† | 36 | 58 | 56 |
| Q148 + ≥2 secondary mutations† | 20 | 24 | 29 |

- Antiviral response was sustained through Week 48[2]
- Difference in response rates between Week 24 and Week 48 was primarily for non-virologic reasons‡[2]

*ITT-E, Snapshot algorithm
†Key secondary mutations were G140A/C/S, L74I and E138A/K/T
‡5 subjects became responders and 15 stopped being responders after Week 24; 4/15 subjects had HIV-1 RNA >50 c/mL at Week 48 and non-compliance; 11/15 subjects re-supressed after Week 48, discontinued for non-compliance, withdrew consent while suppressed, or changed background ART while suppressed[3]

1. Castagna A, et al. J Infect Dis 2014;210:354–62
2. Vavro CL, et al. EUDRW 2014. Abstract O_10
3. ViiV data on file (VIKING-3 48-week Clinical Study Report)

# VIKING-4: PHASE III TRIAL IN TREATMENT-EXPERIENCED, INI-RESISTANT SUBJECTS




•Akil B, et al. EACS 2013. Abstract PE7/3

# Day 8 response (locfdb, itt-e) BY BASELINE dTg FC in $ic_{50}$

| Baseline DTG FC in $IC_{50}$ | VIKING-4 DTG 50 mg BID (N=14) | | VIKING-4 PBO (N=16) | |
|---|---|---|---|---|
| | n | Mean HIV-1 RNA decline, $log_{10}$ c/mL (SD) | n | Mean HIV-1 RNA decline, $log_{10}$ c/mL (SD) |
| 0 to 2.5 | 4 | -1.33 (0.822) | 7 | -0.00 (0.335) |
| >2.5 to 4 | 2 | -1.22 (0.646) | 3 | -0.13 (0.277) |
| >4 to 8 | 5 | -0.89 (0.654) | 4 | -0.02 (0.223) |
| >8 to 10 | 0 | – | 0 | – |
| >10 to 20 | 1 | -0.86 | 1 | -0.06 |
| >20 | 1 | -0.16 | 1 | 0.09 |
| Missing | 1 | -1.82 | 0 | – |

•Akil B, et al. EACS 2013. Abstract PE7/3

# VIKING-4: Day 8 Response by Baseline INI Mutations

| Baseline INI mutation group | VIKING-4 DTG 50 mg BID | | VIKING-4 PBO | |
|---|---|---|---|---|
| | **n** | **Mean* (SD)** | **n** | **Mean* (SD)** |
| Overall | 14† | –1.06 (0.17) | 16 | –0.10 (0.18) |
| | **n** | **Mean (SD)** | **n** | **Mean (SD)** |
| No Q148‡ | 5 | –1.43 (0.745) | 9 | –0.03 (0.325) |
| Q148 + 1§ | 6 | –0.87 (0.587) | 6 | –0.05 (0.182) |
| Q148 + ≥2§ | 3 | –0.90 (0.758) | 1 | 0.09 |

Akil B, et al. Antivir Ther 2015;20:343–8

# Conclusões