I CONGRESSO PARANAENSE DE INFECTOLOGIA

HIV e AIDS ATUALIDADE E FUTURO

O QUE O FUTURO RESERVA ?

- JAN WALTER STEGMANN

LONDRINA MARÇO 2017

CONFLITOS DE INTERESSE

- RESOLUÇÃO 1931/2009 CFM
- RDC 96/2008 ANVISA

Participação congressos/cursos/eventos
Abbot, Bristol, MSD, GSK, Gilead, Roche

Palestrante/apresentador
Abbot, Bristol, MSD

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

HIV E AIDS ATUALIDADE E FUTURO

- O QUE O FUTURO RESERVA

- **PrEP:**
- Potenciais estratégias para prevenção do HIV

- **TERAPEUTICA**
- Novas Formulações
- Novas Estratégias

- **CURA da AIDS**

Quatro Oportunidades para Intervenção

Status	Medida Preventiva	Timing
Não infectado, não exposto	**Comportamento**, intervenções básicas Abstinência (condoms, circumcisão)	Anos
Não infectado, exposto (precoital/coital)	**PrEP**	**Horas**
Não infectado, exposto (postcoital)	PEP	72 horas
Infectado	Tratamento do HIV para reduzir infectividade	Anos

Cohen MS, et al. J Clin Invest. 2008;118:1244-1254.
Cohen MS, et al. J Int AIDS Soc. 2008;11:4.

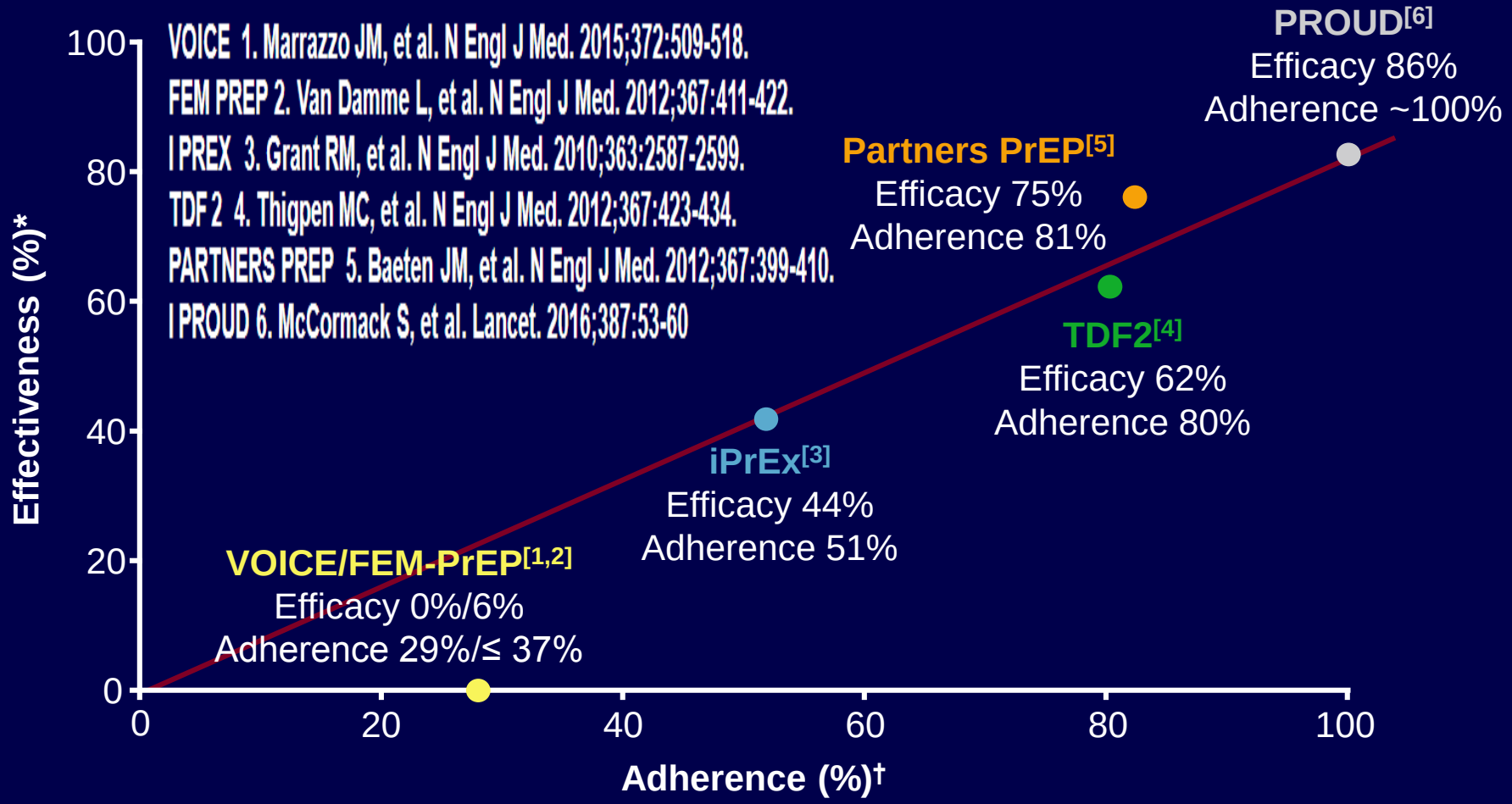
TDF - TENOFOVIR Oral - Base da PrEP: Racional

- Numerosos estudos de fase III PrEP usaram cp TDF oral

- TDF tem várias vantagens para ser preferencial
  - Potencia: potente (todos subtipos HIV), rapidamente ativo
  - Segurança: perfil favoravel, experiencia de longo tempo
  - facilidade: dose unica, sem restrições com alimentos, poucas interações

- TDF/3TC co formulado para uso diário por via oral

Select Daily Oral TDF/FTC PrEP Trials: Effectiveness Improves With Adherence



*Reduction in HIV incidence vs control. †Based on pill counts or the detection of study drug in plasma.

PrEP Is Highly Effective When Taken

- Randomized, placebo-controlled trial[1] or open-label extension[2] in which HIV-uninfected people received once-daily oral TDF/FTC

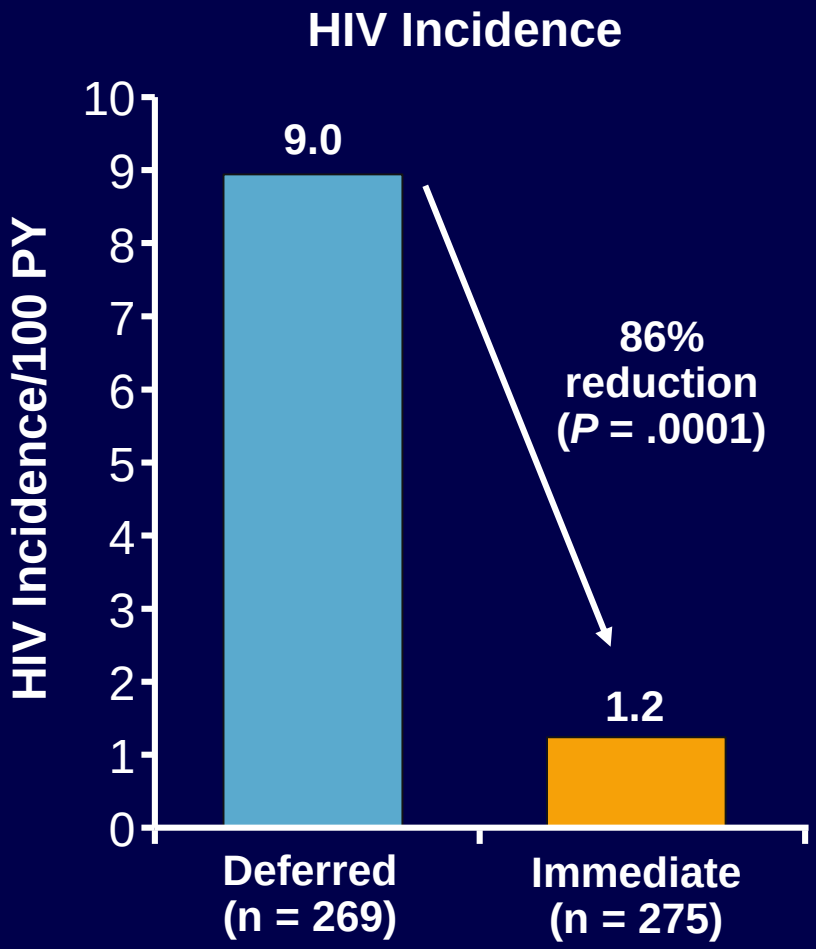
Study	TFV Level*	HIV Acquisition Risk Reduction, %
Partners PrEP[1]	Any detectable	90†
iPrEx OLE[2]	Any detectable to < 2 doses/wk	44‡
	2-3 doses/wk	84‡
	4-6 doses/wk	100‡
	7 doses/wk	100‡

*In plasma (Partners PrEP) or DBS (iPrEx OLE) from people who became infected with HIV during the study or a random subgroup who did not become infected. †Detectable vs no detectable TFV. ‡PrEP vs no PrEP.

1. Baeten JM, et al. N Engl J Med. 2012;367:399-410.
2. Grant RM, et al. Lancet Infect Dis. 2014;14:820-829.

PROUD: Immediate vs Deferred PrEP in High-Risk MSM in "Real World" Trial

- Randomized, open-label trial of daily oral TDF/FTC PrEP in uninfected MSM at high risk for HIV infection in England
  - PrEP: immediate vs deferred for 12 mos
- Fewer new HIV infections with immediate vs deferred PrEP (3 vs 20)
- Risk behaviors similar between arms



McCormack S, et al. Lancet. 2016;387:53-60.

Slide credit: clinicaloptions.com

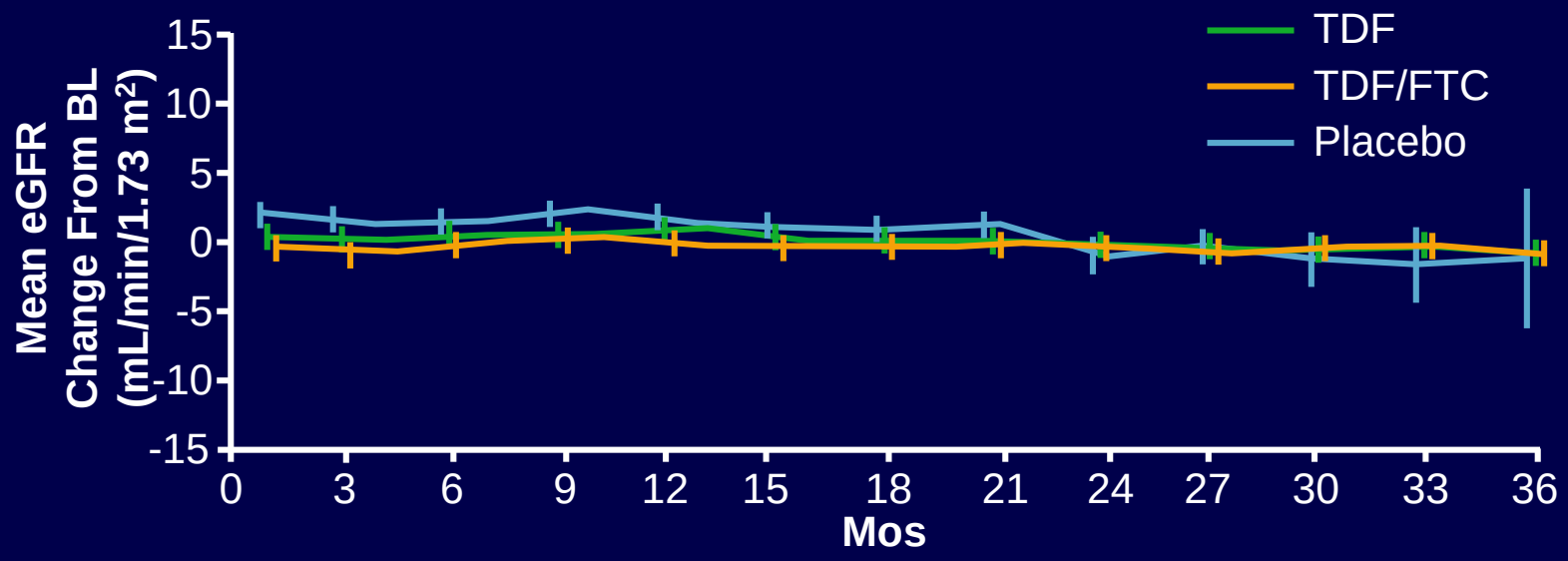
Additional Considerations for PrEP Use? Is TDF/FTC PrEP Safe?

- **Meta-analysis of randomized, placebo-controlled PrEP studies demonstrated** that the risk of any AE or grade 3/4 AEs is not increased for TDF-based PrEP vs placebo[1]
- Bone safety: iPrEx bone mineral density substudy[2,3]
  - High-risk MSM/TGW who received TDF/FTC PO QD PrEP and had dual-energy x-ray absorptiometry assessment (N = 498)
  - Small net decrease in spine and total hip BMD with TDF/FTC vs PBO at Wk 24 (-0.91% and -0.61%, respectively; *P* = .001 for both)
  - **No difference in fracture rate** between groups (*P* = .62)
  - **BMD lost from hip and spine during TDF/FTC use recovered** following discontinuation

1. Fonner VA, et al. AIDS. 2016;30:1973-1983.
2. Mulligan K, et al. Clin Infect Dis. 2015;61:572-580.
3. Grant R, et al. CROI 2016. Abstract 48LB.

PrEP and Renal Safety

- Analysis of eGFR changes with TDF ± FTC PrEP in Partners PrEP (N = 4640)[1]
  - **Over 36 mos of continuous use, PrEP use did not result in a progressive change in renal function**

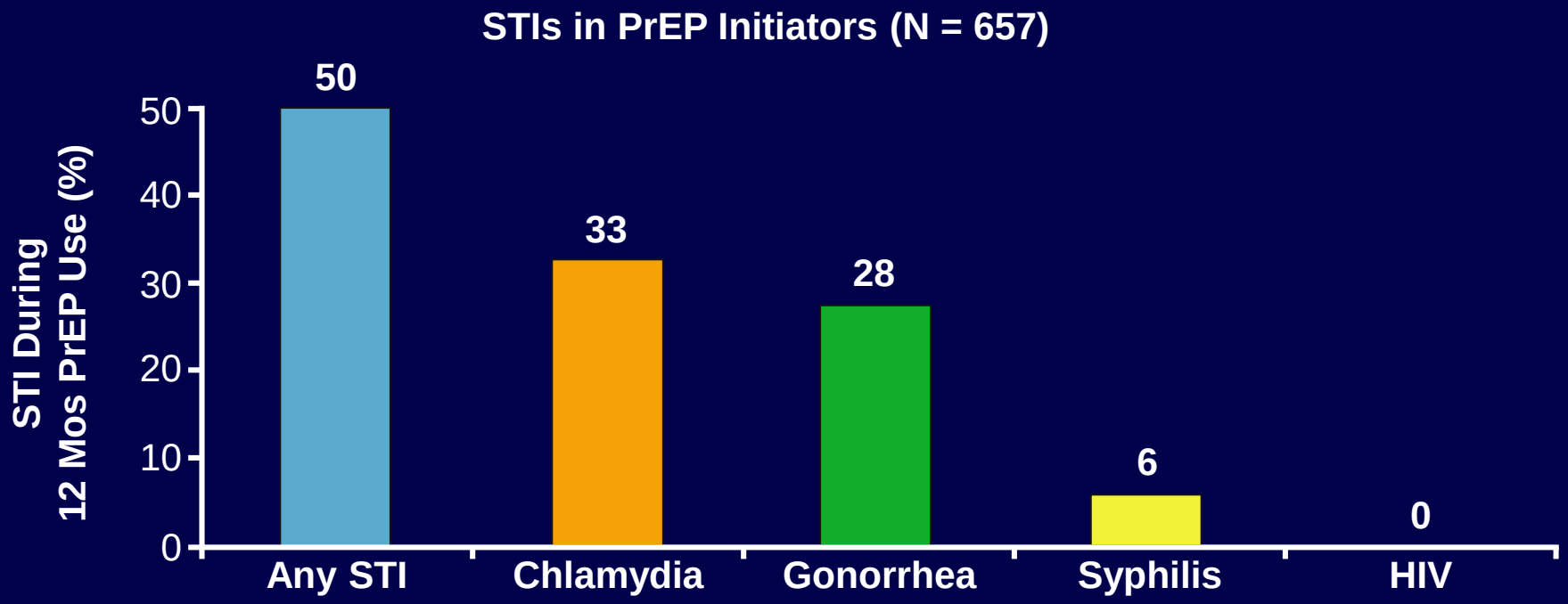


- Analysis of renal function in iPrEx OLE (N = 220): eGFR decrease to < 70 mL/min more frequent at higher levels of TFV exposure among those with **BL eGFR < 90 mL/min** or who were **older than 40 yrs**[2]

1. Mugwanya KK, et al. JAMA Intern Med. 2015;175:246-254.
2. Gandhi M, et al. CROI 2016. Abstract 866.

STIs Will Occur for Persons Using PrEP

- Analysis of HIV/STI incidence in PrEP users in large healthcare system (Kaiser Permanente San Francisco) from 2012 to 2015[1]



- PROUD: similar rates of any STI in 12 mos before starting PrEP (63%) vs during 12 months of PrEP (57%)[2]

1. Volk JE, et al. Clin Infect Dis. 2015;61:1601-1603.
2. McCormack S, et al. Lancet. 2016;387:53-60.

Slide credit: clinicaloptions.com

PrEP

- **QUAIS ESTRATEGIAS TEMOS PARA O FUTURO**

- PrEP “em demanda”
- Drogas V.O. mais seguras
- Drogas injetáveis de Longa Duração
- Anel Vaginal
- Implantes subdermicos
- Vacina

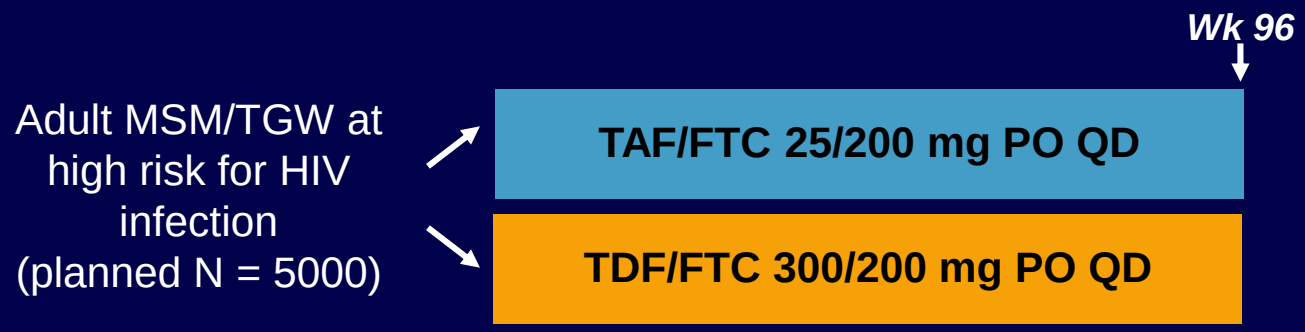
On-Demand (Non-Daily) PrEP Dosing

Study	Design and Findings
IPERGAY[1] ▪ N = 400	▪ **Event-driven oral TDF/FTC vs PBO for high-risk MSM** ▪ Dosing: 2 tablets 2-24 hrs before sex, 1 tablet 24 hrs after first dose, 1 tablet 48 hrs after first dose ▪ **86% reduction in risk with PrEP** vs PBO (*P* = .002) ▪ Plasma TFV detected in 86% of pts in PrEP group (n = 113)
HPTN 067/ ADAPT[2-4] ▪ N = 536	▪ **Once-daily, time-driven, or event-driven oral TDF/FTC for MSM/TGW/women in 3 locations** ▪ Dosing: time driven = 1 dose twice weekly + 1 dose after sex; event driven = 1 dose before and after sex ▪ **Level of complete coverage (adherence) varied by location and population** ▪ In 2 locations, decreased coverage with time/event driven vs once-daily PrEP

1. Molina JM, et al. N Engl J Med. 2015;373:2237-2246.
2. Mannheimer S, et al. IAS 2015. Abstract MOAC0305LB.
3. Holtz TH, et al. IAS 2015. Abstract MOAC0306LB.
4. Bekker L, et al. CROI 2015. Abstract 978LB.

DROGAS MAIS SEGURAS (TDF DISOPROXIL)
TAF/FTC for HIV Prevention

- TAF may offer improved bone/renal safety vs TDF[1]
- TAF: TFV prodrug ALAFENAMIDA
  - TAF/FTC approved in combination with other ARVs for HIV treatment[2]; **not currently approved for PrEP**
  - Systemic TFV levels reduced 90% with TAF 25 mg vs TDF 300 mg[3]
- Randomized phase III PrEP trial now under way[4]



*Plus TDF/FTC placebo tablet QD. †Plus TAF/FTC placebo tablet QD.

References in slidenotes.

Slide credit: clinicaloptions.com

DROGAS INJETÁVEIS DE LONGA DURAÇÃO para prevenção HIV

- May address daily oral tablet adherence issues
- **Cabotegravir**: INSTI formulated as oral tablet and for long-acting intramuscular injection

CAB Trial	Design and Findings
ECLAIR[1] ▪ Phase IIa ▪ N = 127	▪ **CAB LA IM (Q12W) vs PBO IM** for men at low risk for HIV infection ▪ Oral CAB vs PBO phase preceded injection phase ▪ Encouraging results in terms of pt satisfaction and safety
HPTN 083[2] ▪ Phase IIb/III ▪ Planned N = 4500	▪ **CAB LA IM (Q8W after 2 inj. 4 wks apart) vs TDF/FTC PO QD** for MSM/TGW at high risk for HIV infection; trial opening soon ▪ CAB vs TDF/FTC oral phase will precede injection phase

- MK-8591 (EFdA)[3]: NRTI that has shown extended half-life and antiviral activity in early-phase trials

1. Markowitz M, et al. CROI 2016. Abstract 106. 2. ClinicalTrials.gov. NCT02720094. 3. Grobler J, et al. CROI 2016. Abstract 98.

DROGAS INGETÁVEIS DE LONGA DURAÇÃO
Broadly Neutralizing Antibodies (bNAbs) for HIV Prevention

- May be used similarly to other long-acting injectables
- VRC01: monoclonal antibody directed against the HIV-1 CD4 binding site[1]
  - Terminal half-life in PK study: ~ 15 days; demonstrated antiviral activity in HIV-infected pts[1,2]
  - Randomized phase II prevention trials now under way
    - Low-dose/high-dose IV VRC01 or placebo Q8W for adults at high risk for HIV infection
    - MSM/TGW (North/South America) and women (sub-Saharan Africa); planned overall enrollment, N = 4200
- Other bNAbs in development: 3BNC117, 10-1074

ClinicalTrials.gov. NCT02716675. NCT02568215. NCT02824536.

Slide credit: clinicaloptions.com

ANEL VAGINAL HIV Prevention

- Potential for better adherence vs oral PrEP; sustained and controlled drug release
- Dapivirine ring: silicone elastomer vaginal matrix ring containing NNRTI dapivirine

Trials	Design and Findings
MTN-020/ASPIRE[1] and IPM-027/Ring[2] studies ▪ Phase III ▪ N = 4588	▪ **Dapivirine vaginal ring Q4W** + HIV prevention services for sexually active HIV-uninfected African women ▪ Dapivirine ring associated with significant reductions in the risk of HIV infection vs PBO ring (27% to 31%; *P* ≤ .05) ▪ No clinically relevant safety differences between dapivirine and PBO ring groups

1. Baeten JM, et al. N Engl J Med. 2016;[Epub ahead of print].
2. Nel A, et al. CROI 2016. Abstract 110LB.

Additional Emerging HIV Prevention Strategies

Strategy	Findings
Vaccines	▪ HVTN100 vaccine met immunogenic criteria required to move into phase IIb/III efficacy study (HVTN702)[1,2] ▪ Other vaccine concepts in earlier phases of study
Implants	▪ Several approaches using subdermal implant models in preclinical development[3,4]

1. Bekker LG, et al. IAC 2016. Abstract TUAX0102LB.
2. ClinicalTrials.gov. NCT02968849.
3. Gunawardana M, et al. Antimicrob Agents Chemother. 2015;59:3913-3919.
4. Schlesinger E, et al. Pharm Res. 2016;33:1649-1656.

RESUMO

- PrEP Deve fazer parte de qualquer estratégia de prevenção do HIV
- TDF+ FTC/3TC Como terapia oral é segura e efetiva, mas NÃO É 100% PROTETIVA (Resist primária / conc droga)
- Necessário manter cuidados básicos de prevenção e MONITORAR os pacientes : DST contágio HIV

- **ESTRATÉGIAS FUTURAS**
  - Comprimidos em demanda
  - Drogas ingetáveis de longa ação
  - Vacinas
  - Aneis Vaginais/Implantes

TERAPEUTICA Futuro Reserva

- **NOVAS FORMULAÇÕES**

CLASSES EXISTENTES

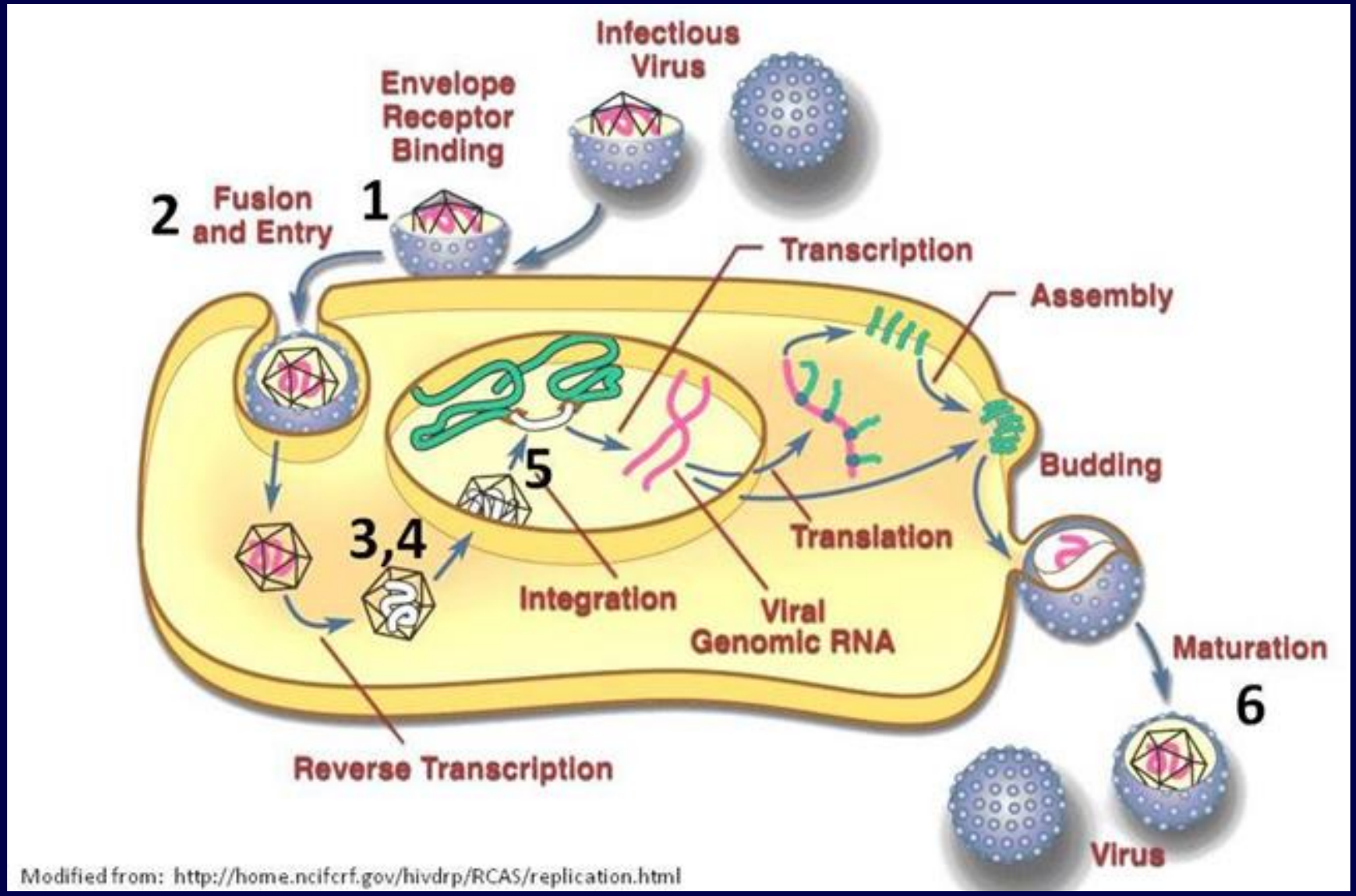
NOVOS ALVOS /NOVAS CLASSES

- **ESQUEMAS TERAPEUTICOS**

INICIAL

MANUTENÇÃO

CICLO HIV ALVOS TRATAMENTO



CLASSES EXISTENTES
INIB. TRANSC. REV. Nucleosideos/tideos

- ITRN GS 9131 pro droga adenosina fase pré clinica atividade ampla subtipos e HIV2 1 tomada dia atividade mantida K65R, M184V, TAMs e inserção T69
- MK 8591 VO / ingetável longa ação (meses) fase pré clinica distribuição tec retal/vaginal/gglios PrEP atividade HIV2

- White KL et al. *GS-9131 is a novel NRTI with activity against NRTI-resistant HIV-1*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 436, 2017.
- Grobler J et al. *MK-8591 concentrations at sites of HIV transmission and replication.* Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 435, 2017.

ITRNN

- Elsulfavirine (VM1500): fase 2b
- dose única diária/ meia vida longa (aprox 8 dias)/ efetividade similar EFV porem mais seguro e tolerável, uso via oral, pro droga VM1500A

- Current phase IIb trial compared efficacy and safety of elsulfavirine plus TDF/FTC vs EFV plus TDF/FTC in treatment-naive patients[1]

- Murphy R, Kravchenko AV, Orlova-Morozova EA, et al. Elsulfavirine as compared to efavirenz in combination with TDF/FTC: 48-week study. Program and abstracts of the 2017 Conference on Retroviruses and Opportunistic Infections; February 13-16, 2017; Seattle, Washington. Abstract 452LB.

- **Doravirine**

- GM Gatell, et al, “Doravirine 100mg QD vs Efavirenz +TDF/FTC in ART-Naive HIV+ Patients: Week 48 Results”. 2016 CROI, Boston, MA.

CLASSES EXISTENTES Inib Protease

- **GSPI1 (**fase pre clin) uso sem booster/dose única diária estudos in vitro potencia > DRV e ATV
- **Nano LPV** fase 1 nanotecnologia: dose < mantem pk

- **Booster PIs**: Cobicistat vs Ritonavir

Characteristic	Finding
Potency	▪ Similar potency associated with ATV/RTV and ATV/COBI when combined with FTC/TDF[1]
Drug interactions	▪ Both inhibit CYP3A and P-gp[2] ▪ **Caution recommended regarding DDIs when switching from RTV to COBI**[3] ▪ RTV an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or UGT1A1; COBI is not
Resistance potential	▪ RTV has antiviral activity; COBI does not[2]

- 1. Gallant JE, et al. J Acquir Immune Defic Syndr. 2015;69:338-340. 2. Marzolini C, et al. J Antimicrob Chemother. 2016;71:1755-1758. 3. COBI [package insert]. 2016. 4 Owen A et al CROI 2017

CLASSES EXISTENTES Inib INTEGRASE

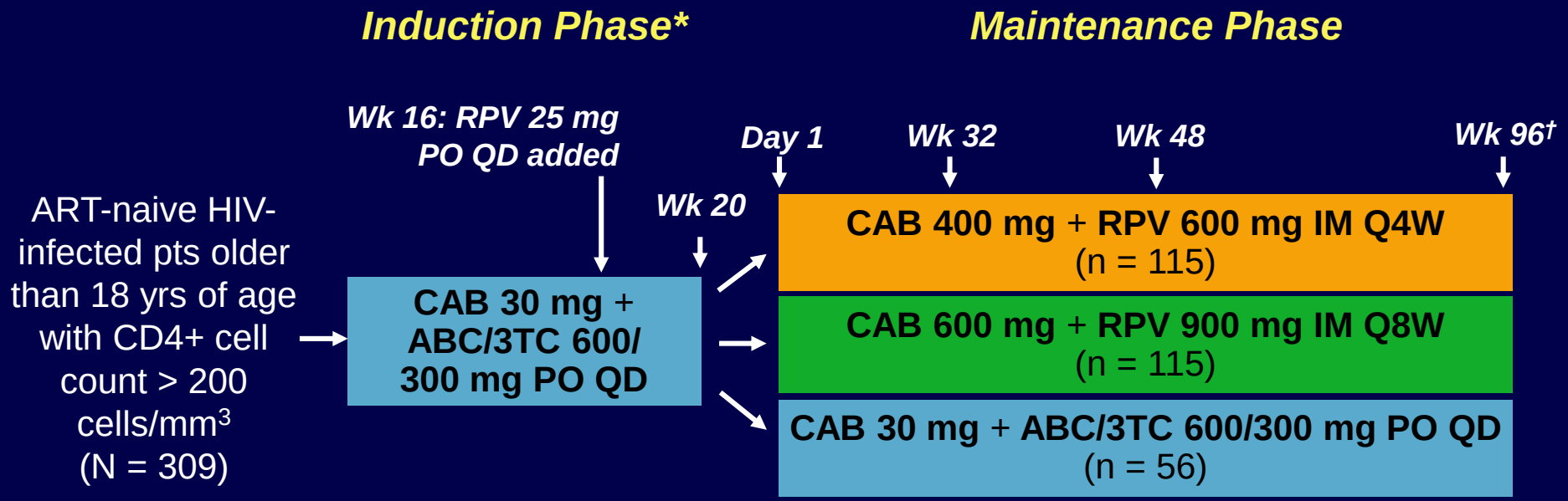
CROI 2017: Integrase Inhibitor **Bictegravir** Matches Dolutegravir for First-Line HIV Treatment

- **Bictegravir**, an investigational integrase inhibitor from Gilead Sciences, was highly potent, well tolerated and worked as well as dolutegravir (Tivcay) in a Phase 2 clinical trial, according to study results presented at
- **Randomized Trial of Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy**
- K Veldsman, J Maritz, S Isaacs, et al. Rapid decline of total HIV DNA in children starting ART within 8 days of birth. Conference on Retroviruses and Opportunistic Infections. Seattle, February 13-16, 2017. Abstract 28.

- **CABOTEGRAVIR**

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- Multicenter, open-label, randomized phase IIb study
  - Primary endpoints: HIV-1 RNA < 50 copies/mL at maintenance Wk 32, PDVF, and safety



*Pts with HIV-1 RNA < 50 copies/mL from Wk 16-20 continued to maintenance phase.
†Pts eligible for Q4W or Q8W LA extension past Wk 96.

Margolis DA, et al. AIDS 2016. Abstract THAB0206LB.

Slide credit: clinicaloptions.com

LATTE-2: Efficacy and Safety Through Maintenance Wk 48

- Virologic efficacy of Q4W/Q8W IM therapy similar to oral therapy

Outcome, % (n)	IM CAB + RPV Q4W (n = 115)	IM CAB + RPV Q8W (n = 115)	Oral CAB + ABC/3TC (n = 56)
Virologic success (HIV-1 RNA < 50 copies/mL)	91 (105)	92 (106)	89 (50)
Virologic nonresponse	< 1 (1)	7 (8)	2 (1)
No virologic data	8 (9)	< 1 (1)	9 (5)

- 99% of ISRs for pts receiving injectable therapy grade 1 (82%) or 2 (17%); none grade 4
  - Most frequent ISRs: pain (67%), nodules (7%), swelling (6%)
  - Reported ISRs decreased over time (86% Day 1, 29% Wk 48)
  - 2/230 pts (< 1%) withdrew for ISRs (both in Q8W arm)
- AEs leading to withdrawal
  - Pooled Q4W/Q8W IM arms, 4%
  - Oral arm, 2%

Margolis DA, et al. AIDS 2016. Abstract THAB0206LB

Slide credit: clinicaloptions.com

NOVAS DROGAS SITIOS DE AÇÃO

- ANTICORPOS MONOCLONAIS
- INIBIDORES MATURAÇÃO
- INIBIDORES CAPSÍDEO
- VACINAS TERAPEUTICAS

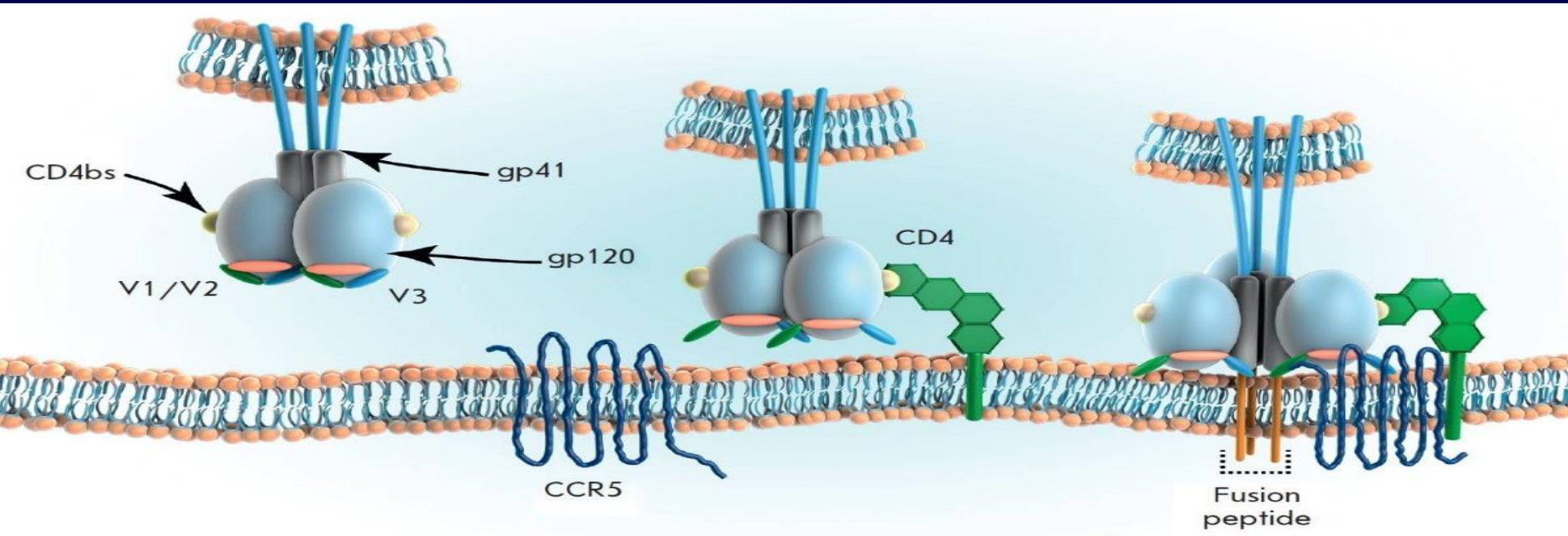
Charlie Sheen Achieves Undetectable Viral Load With Weekly Injectable HIV Treatment

Sheen, who disclosed his HIV status in Nov. 2015, started taking PRO 140 as a study participant in a phase-3 clinical trial that is looking into the drug's safety and effectiveness in humans. In the study, the drug was given without any other HIV antiretroviral drugs to see whether PRO 140 alone was enough to fight HIV and maintain an undetectable viral load. Sheen has been a part of the study for eight months, according to *The Daily Mail*.

- The study administered PRO 140 once every week, but one dose can last up to two months

ANTICORPOS MONOCLONAIS

- São produtos biofarmacêuticos á base de imunoglobulinas modificadas que exercem um efeito específico e controlado sobre um determinado alvo



ANTICORPOS MONOCLONAIS

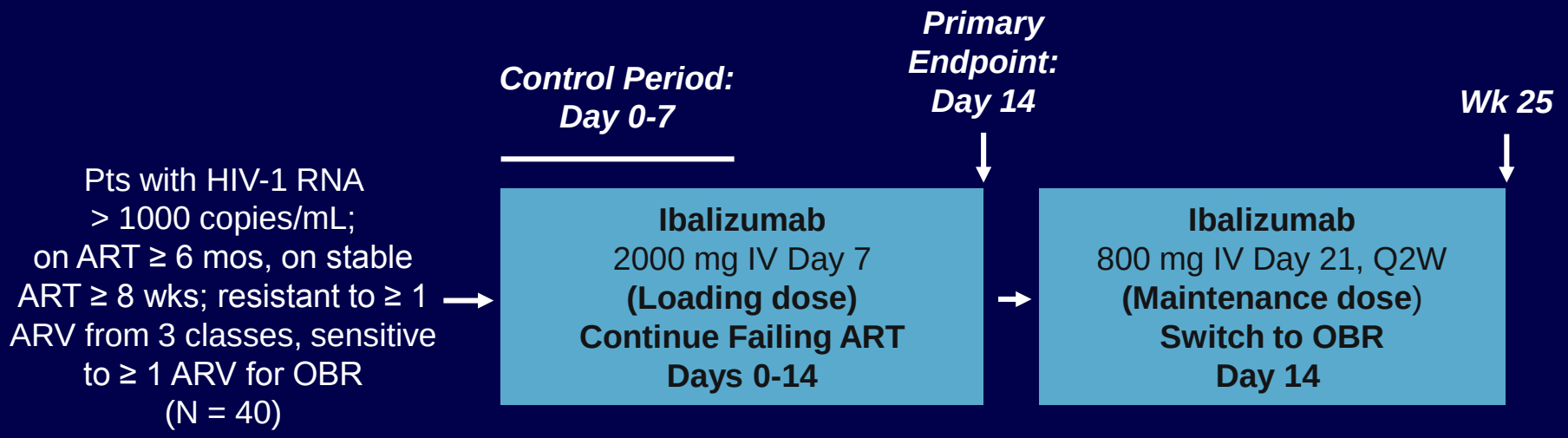
- **IBALIZUMAB** TMB 355 TNX 355
  ALVO CELULA LIGAÇÃO CD4
- USO E.V. (avaliado IM cada 2/4 semanas)
  Combinado esquema ARV otimizado

- **PRO 140** ligação ccr5 EV ou SC potente atividade antiviral manutenção tto como agente único

- Ac Neutralizante **VRC01 e VRC02** ALVO CD4 Gp 160

TMB-301: Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells
- Single-arm, open-label phase III trial
  - Primary endpoint: ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14



- 28% treated with ≥ 10 ARVs; 50% with resistance to all drugs from ≥ 3 classes; 61% with major INSTI resistance in preliminary analysis

Lalezari J, et al. IDWeek 2016. Abstract LB-6.

Slide credit: clinicaloptions.com

TMB-301: Efficacy, Safety of Ibalizumab at Day 14

- Primary efficacy endpoint: HIV-1 RNA reduction at Day 14 after Day 7 ibalizumab loading dose
  - 83% of pts achieved ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14 vs 3% at end of control period
  - 60% of pts achieved ≥ 1.0 $\log_{10}$ HIV-1 RNA decrease at Day 14 vs none at end of control period
- Safety/tolerability
  - No discontinuations for AEs
  - No treatment-related serious AEs

Lalezari J, et al. IDWeek 2016. Abstract LB-6.

ANTICORPO MONOCLONAL LONGA AÇÃO

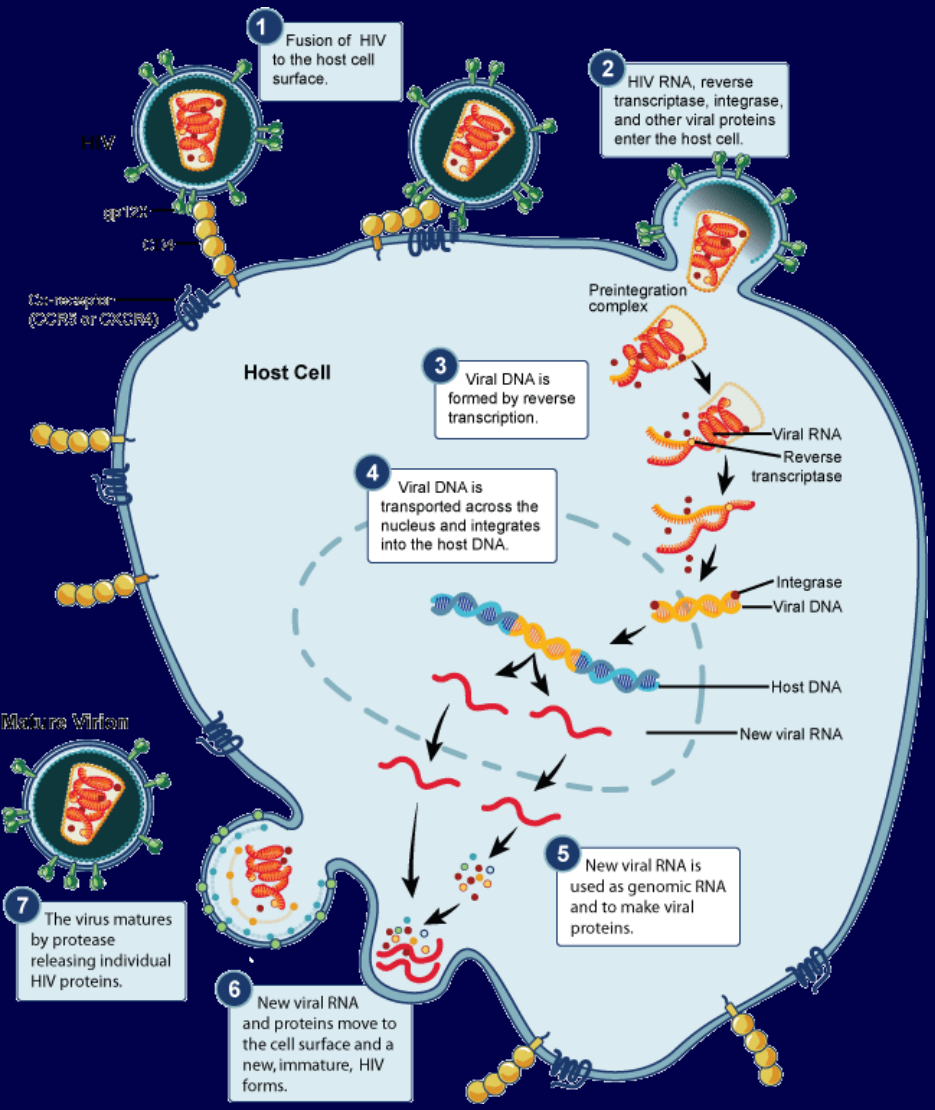
- **PRO 140** blocks CCR5, one of the 2 co-receptors that HIV uses to enter cells, acting like the oral antiretroviral maraviroc (Selzentry)
- An early study showed that a single IV infusion of PRO 140 had potent antiviral activity, and a follow-up study found that weekly subcutaneous injections of PRO 140 reduced viral load significantly more than placebo.
- CD01, a Phase 2b trial of PRO 140 as maintenance therapy for people who had achieved viral suppression on standard combination ART.

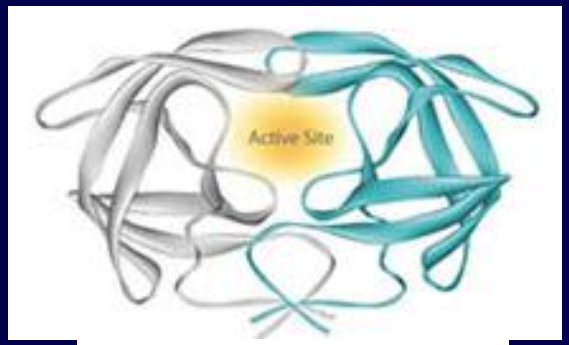
- J Lalezari, K Dhody, U Kowalczyk, et al. PRO140 single-agent maintenance therapy for HIV-1 infection: a 2-year update. Conference on Retroviruses and Opportunistic Infections. Boston, February 22-25, 2017. Abstract 437.

ANTICORPOS NEUTRALIZANTES

- **Passive immunization with HIV-1-neutralizing monoclonal antibodies (mAbs) is being considered for prevention and treatment of HIV-1 infection. As therapeutic agents, mAbs could be used to suppress active virus replication, maintain suppression induced by antiretroviral therapy (ART), and/or decrease the size of the persistent virus reservoir.**
- **VRC01 VRC02**
- **UB-421 [450LB] (yet *another* monoclonal antibody that blocks viral entry) CROI 2016**
- A PHASE 2 OPEN-LABEL TRIAL OF ANTIBODY UB-421 MONOTHERAPY AS A SUBSTITUTE FOR HAART **Author(s):** Chang-Yi Wang[1], Wingwai Wong[2], Hung-Chin Tsai[3], Yen-Hsu Chen[4], Mei-June Liao[5], Shugene Lynn[61]United Biomed, Inc, Hauppauge, NY, USA,[2]Taipei Veterans General Hosp, Taipei, Taiwan,[3]Kaohsiung Veterans General Hosp, Kaohsiung, Taiwan,[4]Kaohsiung Med Univ and Hosp, Kaohsiung, Taiwan,[5]United Biopharma, Inc, Hsinchu, Taiwan,[6]UBI Asia, Hsinchu, Taiwan

INIBIDORES DE MATURAÇÃO





INIBIDORES MATURAÇÃO-

- BEVERIMAT POLIMORFISMOS gag 40% RESISTENCIA PRIMÁRIA
- BMS 955179 EFEITOS ADVERSOS (GI)

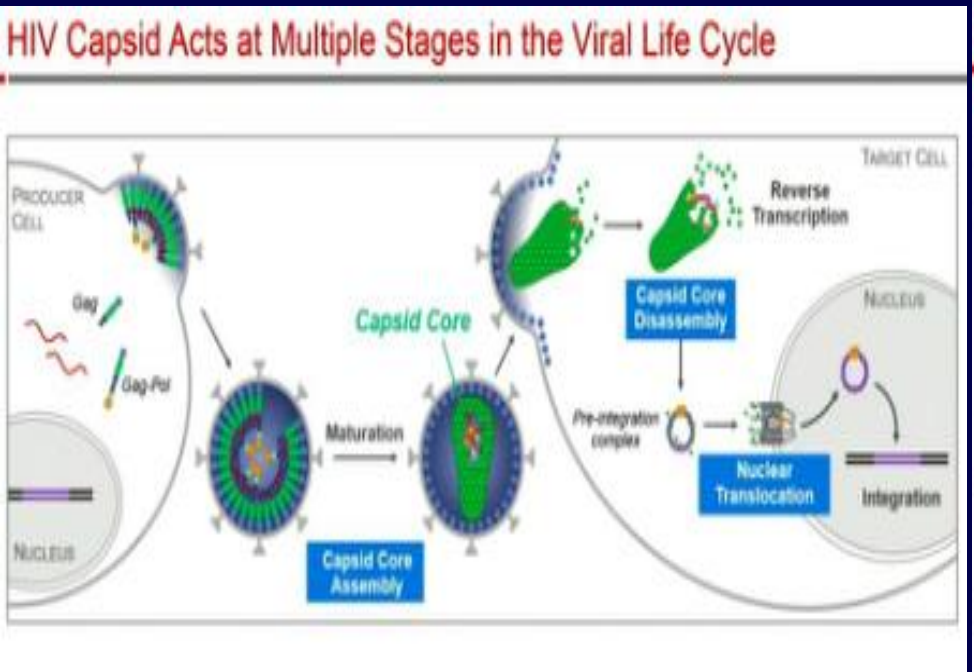
- BMS-955176
- BMS 986 173

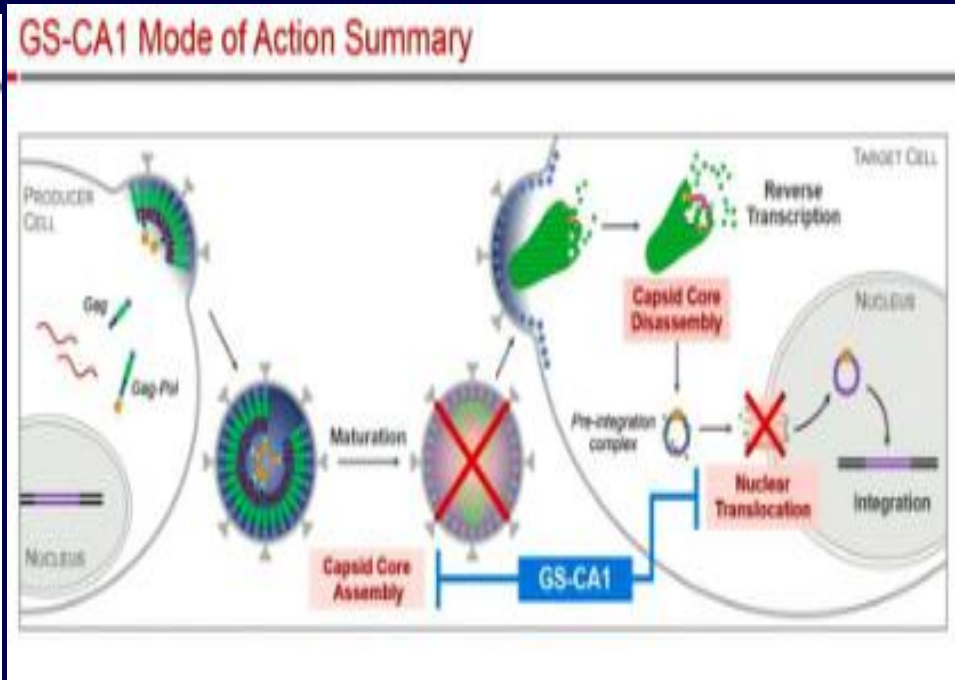
- Press Release, dated October 23, 2015. Complete Phase 2a Study of HIV-1 Investigational Maturation Inhibitor Demonstrates Positive Results for Therapy Designed to Attack Virus Differently Than Existing Treatments. Available at: http://news.bms.com/press-release/complete-phase-2a-study-hiv-1-investigational-maturation-inhibitor-demonstrates-positi. Last accessed on September

INIBIDOR CAPSIDEO- **BS-CA1**

Interferem na montagem e desmonte do capsideo (estrutura que contem enzimas e material genético do vírus) atua p24 (proteína do capsídeo) em múltiplas etapas Potencia alta atividade todos subtipos e HIV 2 .

- Tse WC et al. *Discovery of novel potent HIV capsid inhibitors with long-acting potential*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 38, 2017.





NOVOS ALVOS FUTURO

- **Design and In Vivo Characterization of Immunoconjugates Targeting HIV gp160.**

- Pincus, S.H.; Song, K.; Maresh, G.A.; Frank, A.; Worthylake, D.; Chung, H.K.; Polacino, P.; Hamer, D.H.; Coyne, C.P.; Rosenblum, M.G.; Marks, J.W.; Chen, G.; Weiss, D.; Ghetie, V.; Vitetta, E.S.; Robinson, J.E.; Hu, S.L Rev. Journal of Virology 2017 Vol. 91 Nro. 3

- **A New Class of Allosteric HIV-1 Integrase Inhibitors Identified by Crystallographic Fragment Screening of the Catalytic Core Domain.**

- Patel, D.; Antwi, J.; Koneru, P.C.; Serrao, E.; Forli, S.; Kessl, J.J.; Feng, L.; Deng, N.; Levy, R.M.; Fuchs, J.R.; Olson, A.J.; Engelman, A.N.; Bauman, J.D.; Kvaratskhelia, M.; Arnold, E.
  Rev. Journal of Biological Chemistry 2016 Vol. 291 Nro. 45 Página: 23569 - 23577

- **Novel Acylguanidine-Based Inhibitor of HIV-1.**

- Mwimanzi, P.; Tietjen, I.; Miller, S.C.; Shahid, A.; Cobarrubias, K.; Kinloch, N.N.; Baraki, B.; Richard, J.; Finzi, A.; Fedida, D.; Brumme, Z.L.; Brockman, M.A.
  Rev. Journal of Virology 2016 Vol. 90 Nro. 20 Página: 9495 - 508

NOVAS ABORDAGENS/ESQUEMAS TERAPEUTICOS

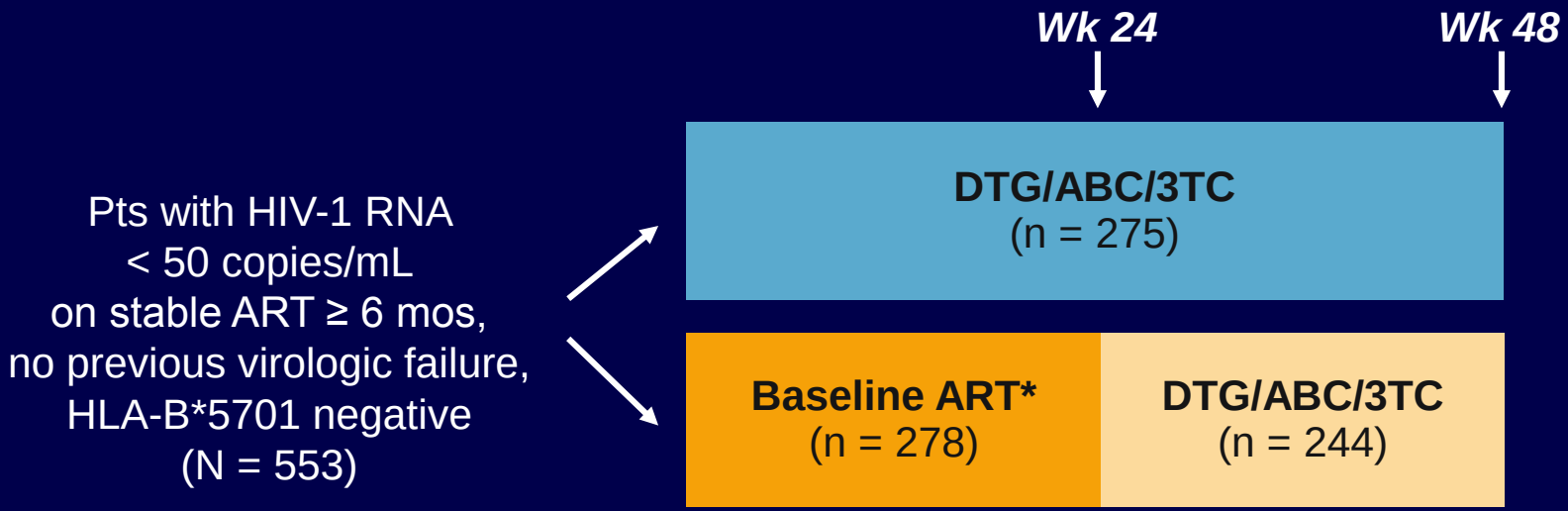
PACIENTES EM TRATAMENTO ESTABILIZADOS

- **SIMPLIFICAÇÃO DO TRATAMENTO**

- 1 COMODIDADE
- 2 TOXICIDADE

COMODIDADE STRIIVING: Switch From Suppressive ART to Fixed-Dose DTG/ABC/3TC

- Multicenter, randomized, open-label phase IIIb study
  - Conducted in US, Canada, and Puerto Rico
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24



*Containing 2 NRTIs plus NNRTI, PI, or INSTI.

Lake J, et al. AIDS 2016. Abstract THAB0203.

Slide credit: clinicaloptions.com

STRIIVING: Virologic Outcomes at Wks 24 and 48

- Similar virologic response rates with switch to DTG/ABC/3TC vs continued baseline ART at Wk 24 primary endpoint

Wk 24 Outcome, %	DTG/ABC/3TC (n = 275)	Baseline ART (n = 278)
Virologic success (HIV-1 RNA < 50 c/mL)	85	88
Virologic nonresponse	1	1
No virologic data	14	10

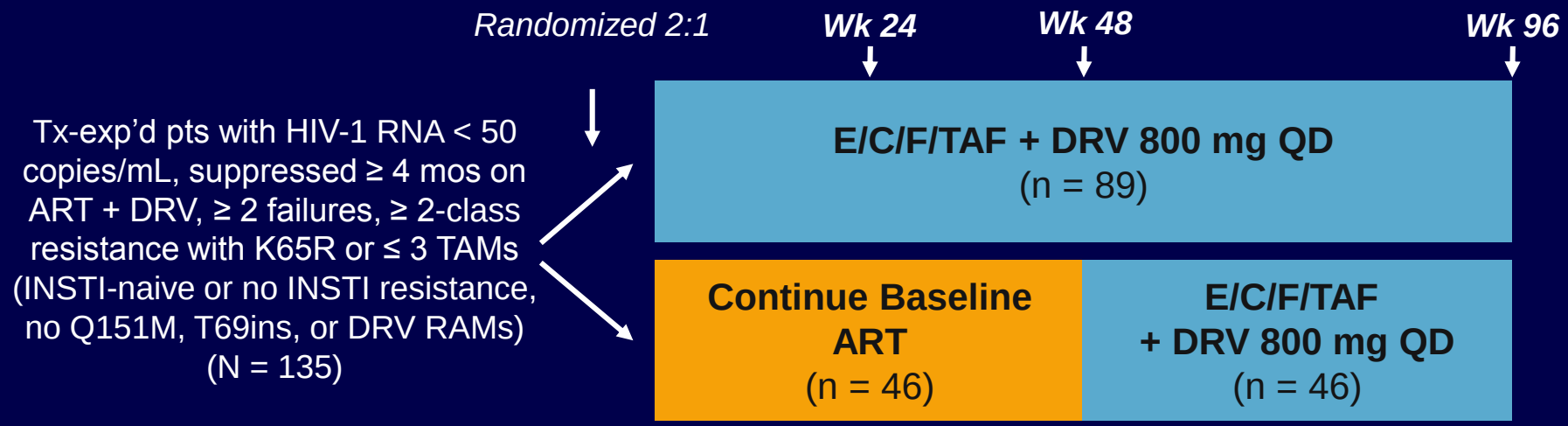
- In pts switched to DTG/ABC/3TC at randomization, 83% maintained virologic suppression through Wk 48
- In pts switched from baseline ART to DTG/ABC/3TC at Wk 24 (n = 244), 92% maintained virologic suppression from Wk 24 to Wk 48
- No cases of protocol-defined virologic failure
  - 1 pt in early switch arm (< 1%) and 3 pts in post-switch BL ART arm (1%) had HIV-1 RNA ≥ 50 c/mL at Wk 48 but all resuppressed to < 50 c/mL

Lake J, et al. AIDS 2016. Abstract THAB0203.

Slide credit: clinicaloptions.com

292-0119: Switch from Multitablet Regimen to Simpl. Elvitegravir/Cobistat/FTC/TAF + DRV

- Randomized, open-label, multicenter phase III switch trial[1,2]
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24
  - Baseline: median 5 pills/day; 2 class resistance, 71%; 3 class, 24%



- Current analysis evaluated **Wk 48 efficacy** by baseline resistance profiles obtained from historic genotypic reports

1. Margot N, et al. HIV Glasgow 2016. Abstract O123.
2. Huhn GD, et al. J Acquir Immune Defic Syndr. 2016;[Epub ahead of print].

Slide credit: clinicaloptions.com

Switch to Simplified E/C/F/TAF + DRV: Virologic Outcomes at Wks 24 and 48

- At Wk 48, virologic efficacy of switch to E/C/F/TAF + DRV noninferior and statistically superior to continuing baseline regimen (*P* = .004)[1]

Outcome, %	E/C/F/TAF + DRV (n = 89)	Continue Baseline ART (n = 46)
At Wk 24[2]		
▪ Virologic success	97	91
▪ Virologic failure	2	0
▪ No data	1	9
At Wk 48[1,2]		
▪ Virologic success	95	76
▪ Virologic failure	2	11
▪ No data	3	13

1. Margot N, et al. Glasgow 2016. Abstract O123.
2. Huhn GD, et al. J Acquir Immune Defic Syndr. 2016;[Epub ahead of print].

TERAPEUTICA - TOXICIDADE

- **MUDANÇA DE CLASSE DO ANTIRETROVIRAL**
- EVITAR CLASSES/DROGAS COM MAIOR TOXICIDADE
- ITRN/t

- **MUDANÇA DO ANTIRETROVIRAL**
- TENOFOVIR

SIMPLIFICAÇÃO DO INICIO TRATAMENTO

- EVITAR **ITRN** CLASSE COM MAIOR TOXICIDAD

- RAL + DRV/R

- 1. Taiwo B, Zheng S, Gallien S, et al; ACTG A5262 Team. Results from a single-arm study of DRV/r + RAL in treatment-naive HIV-1-infected patients (ACTG A5262). In: Program and abstracts of the 18th Conference on Retroviruses and Opportunistic Infections; February 27-March 2, 2011; Boston. Abstract 551.

- 2. Bedimo R, Drechsler H, Turner D, et al. RADAR study: raltegravir combined with boosted darunavir has similar safety and antiviral efficacy as tenofovir/emtricitabine combined with boosted ritonavir in antiretroviral-naive patients. In: Program and abstracts of the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention (IAS 2011); July 17-20, 2011; Rome. Abstract MOPE214.

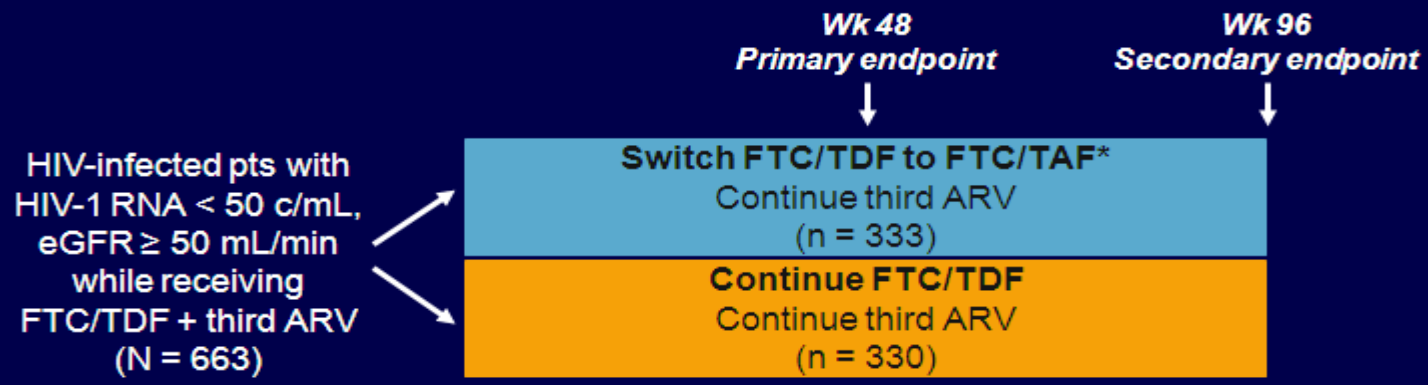
- MUDANDO PARADIGMA **INICIO TTO 2 DROGAS**

TOXICIDADE

- *TDF tenofovir disoproxil fumarate*
- *TAF, tenofovir alafenamide;*

GS-1089: Switch from Suppressive TDF- to TAF-Containing ART

- Randomized, double-blind, active-controlled phase III trial
  - Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48 by ITT FDA snapshot; noninferiority margin 10%
  - Current analysis includes Wk 96 secondary endpoints: virologic suppression, renal/bone safety biomarkers, and safety/tolerability

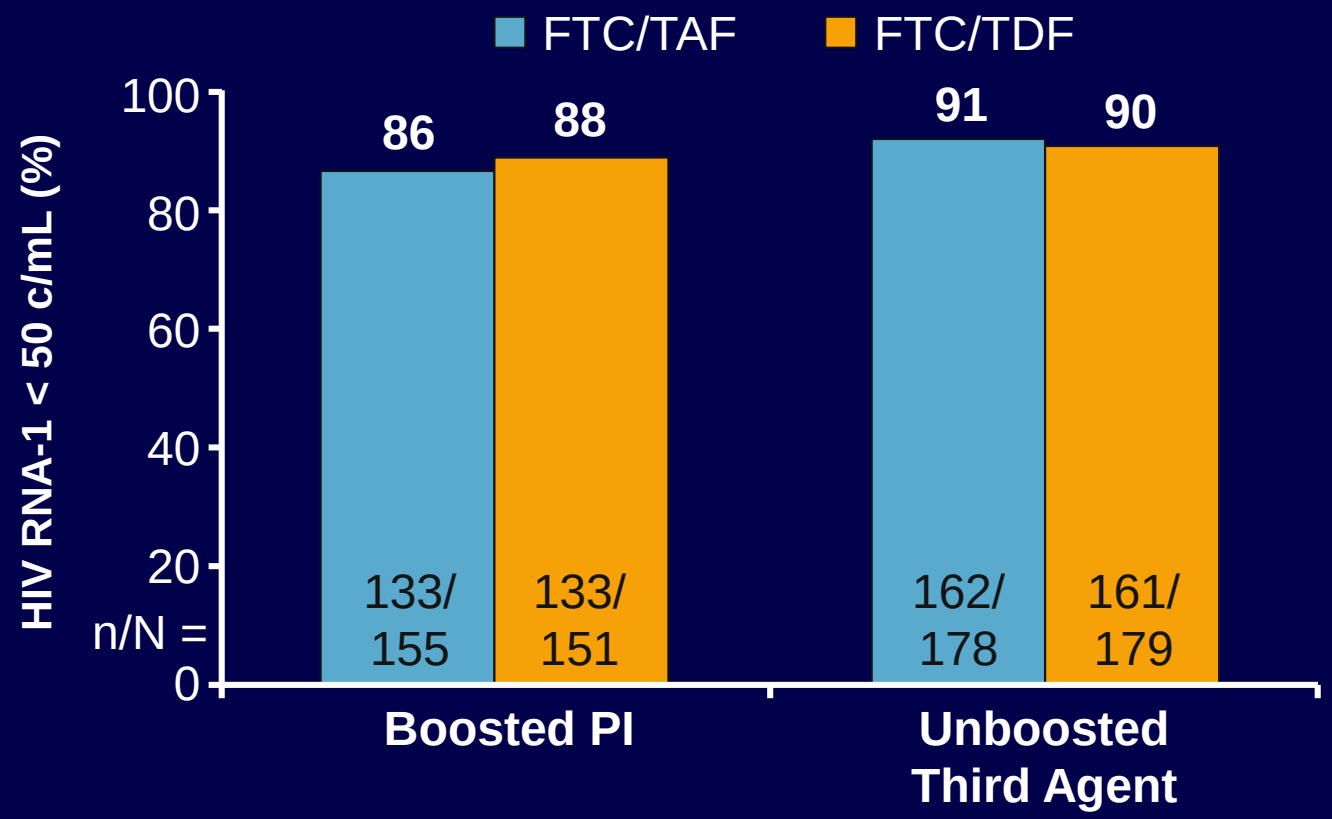


*FTC/TAF dosing: 200/10 mg with boosted PIs; 200/25 mg with unboosted third drug.

Raffi F, et al. HIV Glasgow 2016. Abstract O125.

Switch From TDF- to TAF-Containing ART: Virologic Efficacy at Wk 96 by Third Agent

- Comparable virologic success rates by third agent, independent of NRTI pair

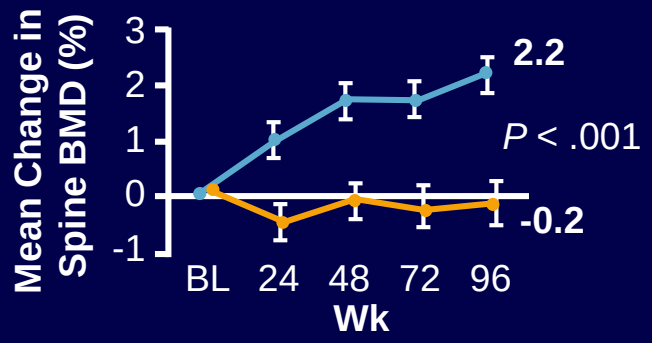


Raffi F, et al. HIV Glasgow 2016. Abstract O125.

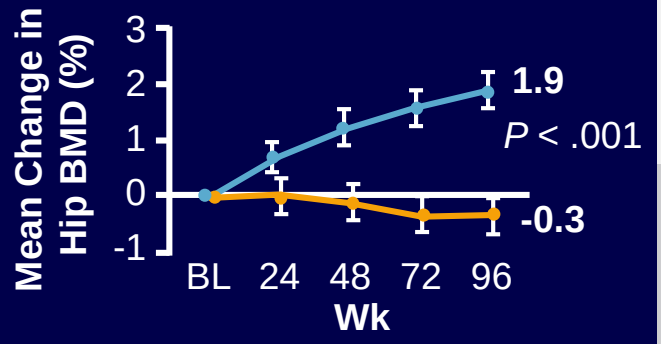
Slide credit: clinicaloptions.com

Switch From TDF- to TAF-Containing ART: Safety Outcomes at Wk 96

- Safety signals and changes in bone, renal biomarkers, and lipids consistent with other TDF-to-TAF switch studies



FTC/TAF 321 310 300 294 287
FTC/TDF 320 310 306 297 292



FTC/TAF 321 309 300 293 288
FTC/TDF 317 305 303 296 289

Change From Baseline to Wk 96*	Boosted PI + FTC		Unboosted Third Agent + FTC	
	TAF (n = 155)	TDF (n = 151)	TAF (n = 178)	TDF (n = 179)
Median change in eGFR, mL/min	+9.3	+4.2	+10.6	+3.3
Median % change in marker				
▪ Urine protein:Cr	-27.2	-1.8	-25.6	+7.8
▪ Urine albumin	-1.3	+21.7	+5.0	+29.2
▪ Urine RBP:Cr	-5.5	+36.5	-2.0	+49.9
▪ Urine β2M:Cr	-28.2	+41.8	-31.9	+51.5
Mean % change in BMD				
▪ Spine	+2.03	-0.49	+2.26	+0.10
▪ Hip	+1.82	-0.28	+1.88	-0.38

*All treatment arm differences significant ($P \leq .005$).

Raffi F, et al. HIV Glasgow 2016. Abstract O125.

Slide credit: clinicaloptions.com

CONCLUSÕES
O QUE ESPERAR NO FUTURO

- **TRATAMENTOS CADA VEZ MENOS TÓXICOS**
- MEDICAMENTOS COFORMULADOS

  - COMODIDADE E TOLERABILIDADE

  DROGAS DE AÇÃO PROLONGADA

  - DROGAS INJETÁVEIS

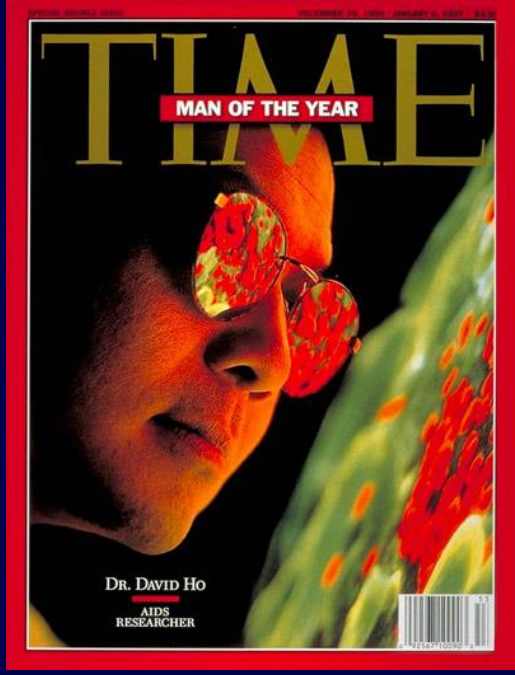
- **DROGAS MAIS POTENTES** - NOVOS ALVOS

  - BARREIRA GENÉTICA

- MULTIPLAS POSSIBILIDADES DE ASSOCIAÇÃO

  - AÇÃO CONTRA VIRUS RESISTENTES

CURA DA AIDS



"Mississippi Baby"

- AONDE ESTAMOS
- PERSPECTIVAS

CURA DA AIDS

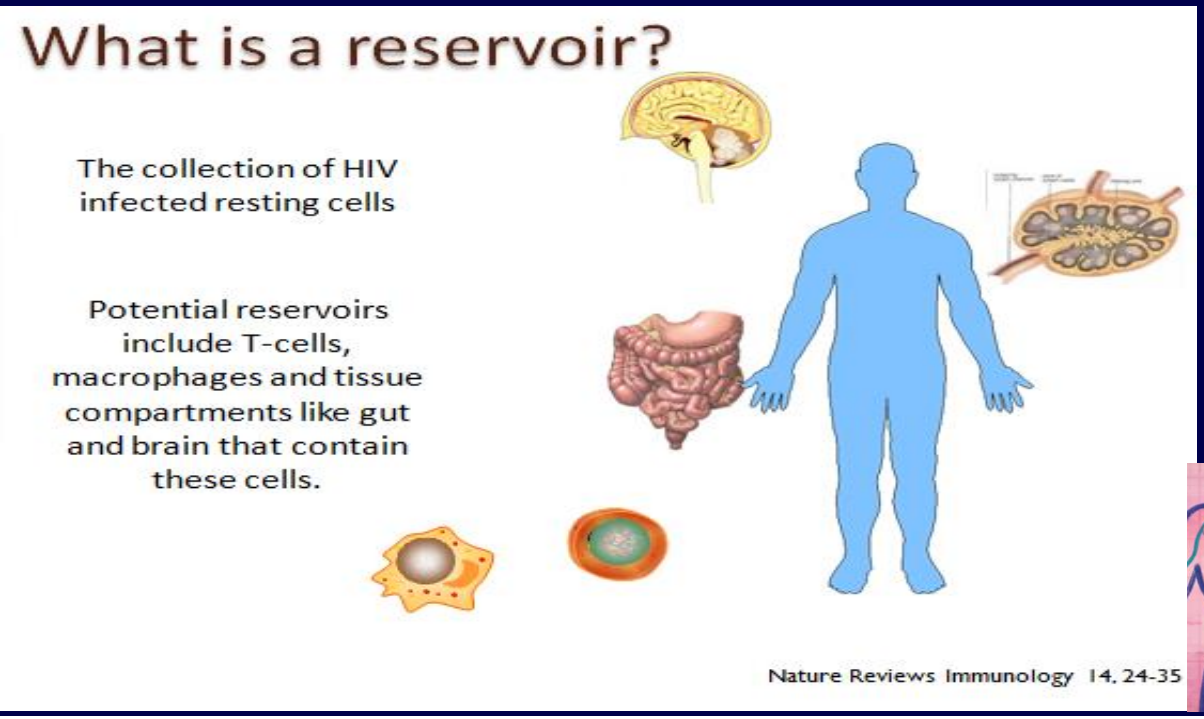
- VIVER SEM TRATAMENTO
- AUSENCIA DE SINTOMAS
- SEM DANO IMUNOLÓGICO
- NÃO TRANSMITIR VIRUS A OUTROS
- ERRADICAÇÃO VIRAL COMPLETA

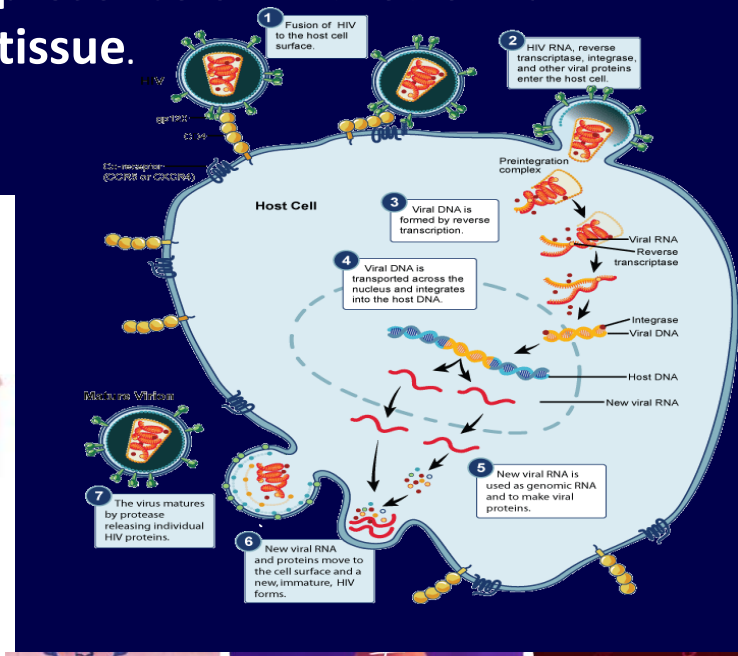
- **TIPOS CURA**
- ESTERELIZANTE – ERRADICAÇÃO
- FUNCIONAL - REMISSÃO

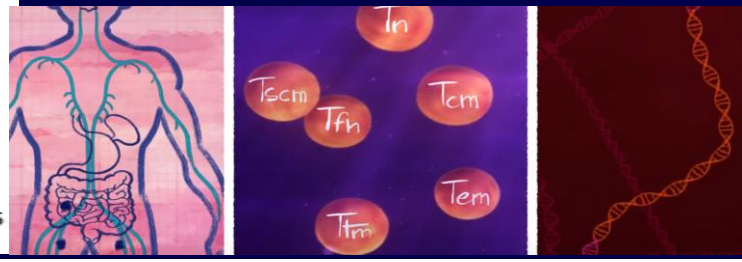
IMPEDIMENTO CURA RESERVATÓRIOS DO HIV CELULAS LATENTES/REPOUSO

- Active reservoirs are cells that produce virus in the presence of Antiretroviral Therapy. Generally these reservoirs are found in the tissue.

- -LATENT RESERVIRS RESTING CELS







Descours B et al. CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses. Nature 2017 Mar 15; [e-pub]. (http://dx.doi.org/10.1038/nature21710)

ESTRATÉGIAS DO TRATAMENTO

- TRATAMENTO PRECOCE
- ELIMINAR RESERVATÓRIOS VIRAIS
- INTENSIFICAR TRATAMENTO ARV
- TERAPIA GENICA / TRANSPLANTE ??
- VACINAS TERAPEUTICAS

TRATAMENTO PRECOCE

- **CORTE DE VISCONTI** Virological and Immunological Studies in CONtrollers after Treatment Interruption. Now a study from France has found 14 adult patients who also started a course of ART soon after infection, who subsequently stopped it, and have not had to re-start because they have largely – and in eight cases completely – maintained undetectable viral loads for at least four years after stopping therapy

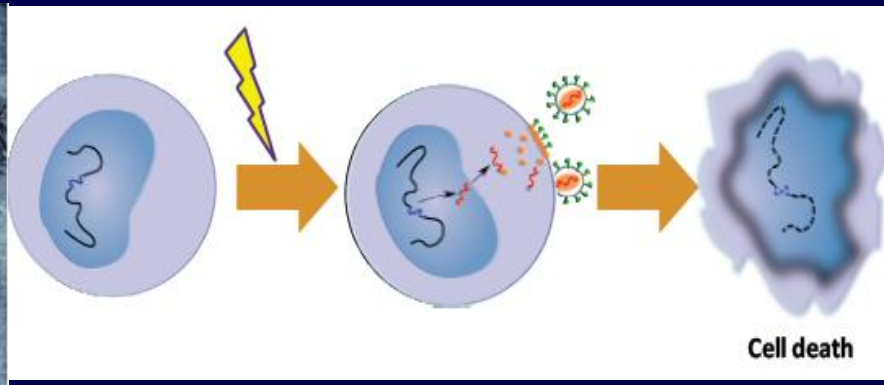
- **SPARTAC** (Short Pulse Antiretroviral Therapy at Acute Seroconversion) study, which compared the effect of 0, 12, or 48 weeks of ART initiated during acute HIV infection

- Sáez-Cirión A et al. *Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy: ANRS VISCONTI study.* PLOS Pathogens, 9(3): doi:10.1371/journal.ppat.1003211, 2013

- Fidler S et al. *The effect of short course ART in primary HIV infection. Final results from an international randomised trial SPARTAC.* Sixth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Rome, abstract WELBX06, 2011

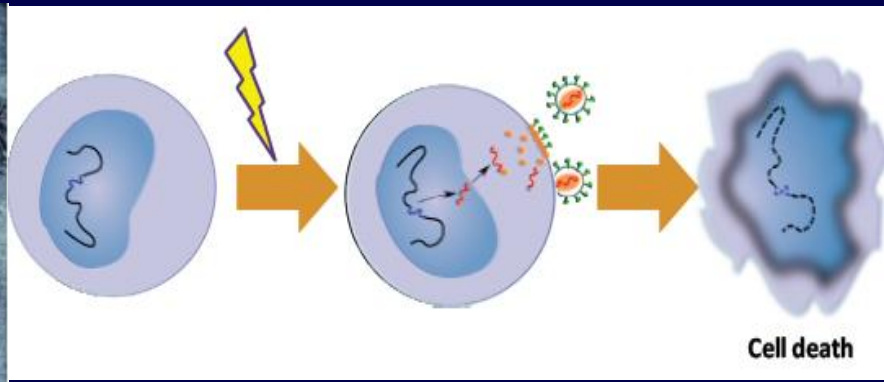
ELIMINAR RESERVATÓRIOS VIRAIS

- “kick and kill”, algo como chutar e matar

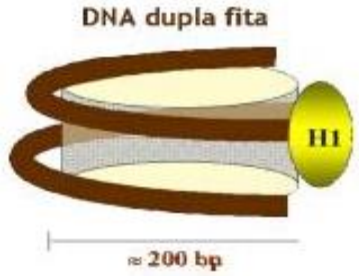


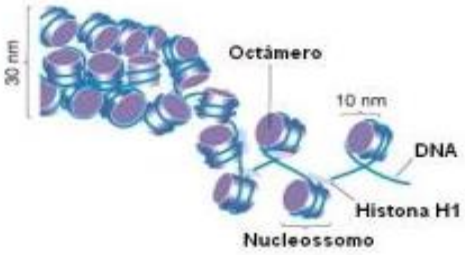
ELIMINAR RESERVATÓRIOS VIRAIS

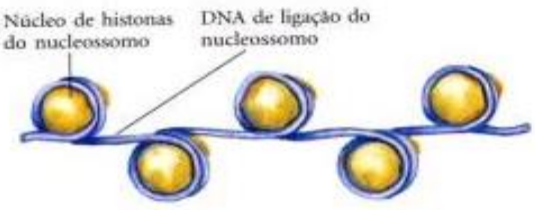
- “kick and kill”, algo como chutar e matar

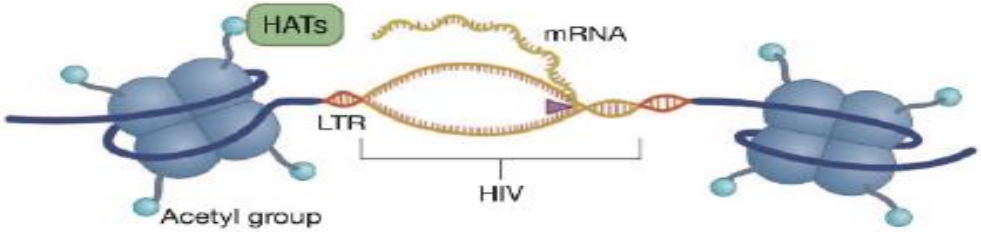


Inibidores Histonas Desacetilases









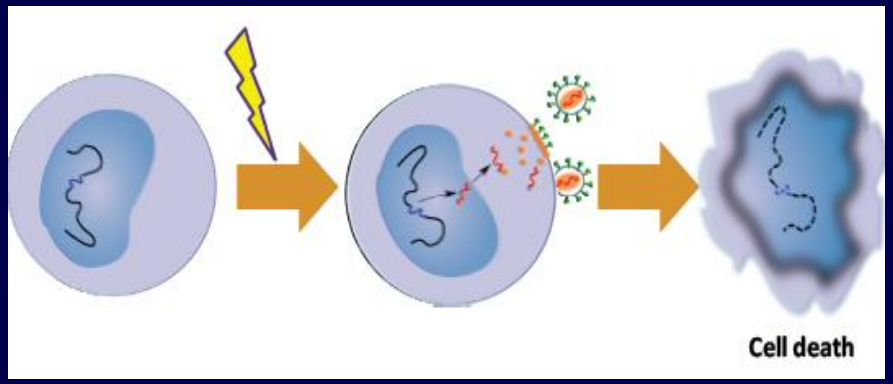
ELIMINAR RESERVATÓRIOS VIRAIS
Inibidores Histonas Desacetilases

- Vorinostat Romidepsin Acido Valproico Sais de ouro

TLR7- Agonist Bromodomains Ingenol Nicotinamida

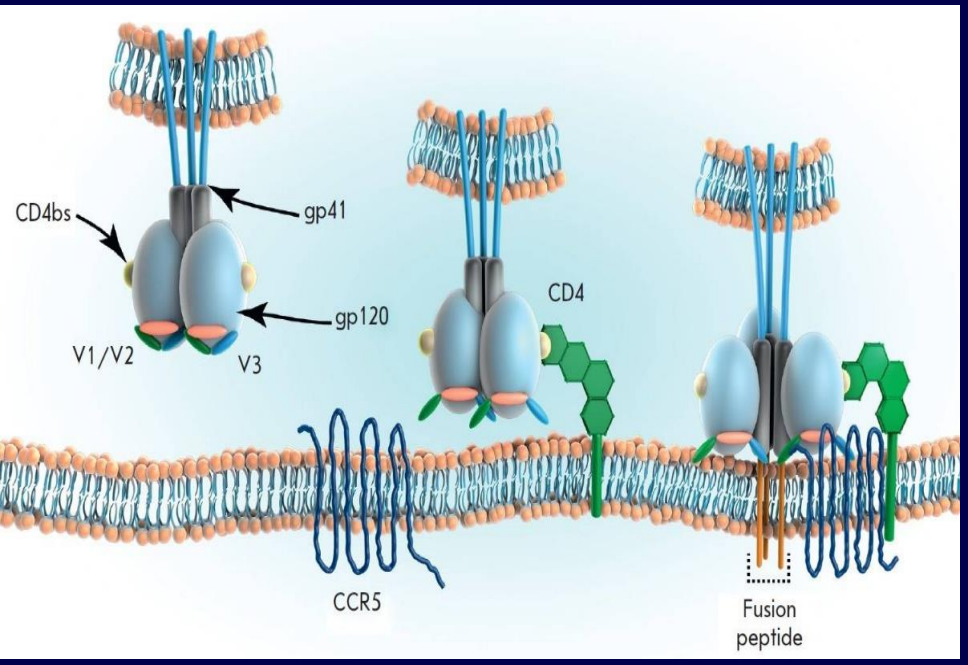
INTENSIFICAR

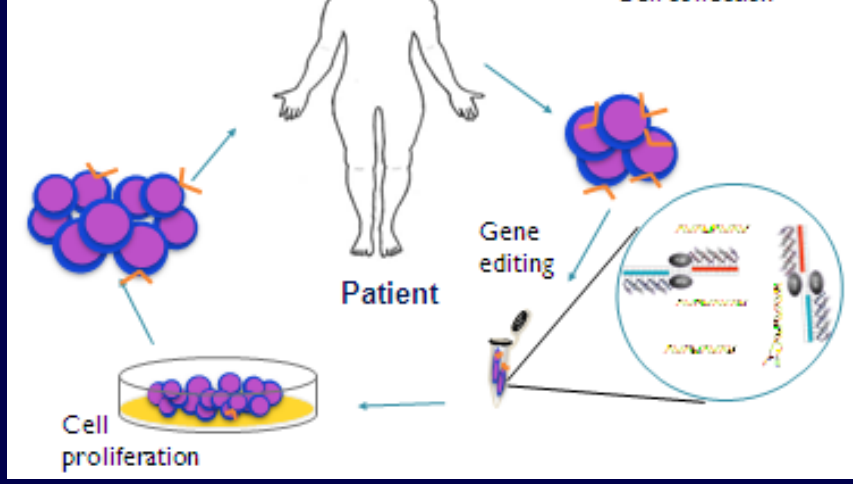
TRATAMENTO



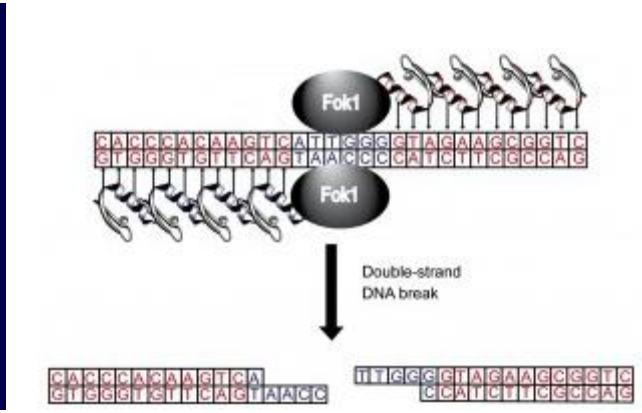
Esquema otimizado + dolutegravir e maraviroc

TERAPIA GÊNICA





zinc finger nuclease



1. Tebas, P. *et al. New Engl. J. Med.* **370**, 901–910 (2014).

TRANSPLANTE MEDULA DOADOR POLIMORFISMO ALELO 32

VACINA TERAPEUTICA

- ●**Racional:** Reforçar ou criar nova e mais efetiva resposta imune a**o HIV em pessoas vivendo com HIV**
- ●Gerar resposta imune adaptiva prolongada ao HIV, que pode continuar a controlar o virus sem medicação
- Localizar e destruir os virús que se evadem da medicação

- Safety and Efficacy of Romidepsin and the Therapeutic Vaccine **Vacc-4x** for Reduction of the Latent HIV-1 Reservoir (REDUC)
- **THE LANCET HIV** Volume 3, No. 10, e463–e472, October 2016

- VACINA CELULAS DENDRITICAS

Quando encontraremos a Cura para HIV?

"People often ask me this," said Steve Deeks, M.D., "and honestly -- I have no idea. But I'm hoping we'll have a regimen -- a combination that's viable and testable, by the time the current funding of this institute is over, in the next few years. That's an optimistic perspective,"

QUESTÃO ÉTICA

DESCONHECIMENTO DE TODA IMUNOLOGIA RELACIONADO AO HIV, POUCOS CENTROS CAPAZES DE EXECUTAR ESSE TRATAMENTO

É LICITO SUBMETER PACIENTES QUE PODEM SER CONTROLADOS ADEQUADAMENTE , A TRATAMENTOS EXPERIMENTAIS E/OU COM RISCO PESSOAL

OBRIGADO

- JWSTEGMANN@UEL.BR
- CTA: 3378-0146 / 3379-0180

I CONGRESSO PARANAENSE DE

INFECTOLOGIA

CPinf 2017

31 DE MARÇO A 1º DE ABRIL