
# Stratégie ARV

Laurence Morand-Joubert,
Isabelle Pellegrin
Pierre De Truchis

# Les stratégies de lutte contre le VIH: chronologie

*Trithérapie: l'arsenal thérapeutique traditionnel depuis 1996*

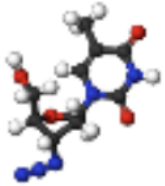


**1996**

**2008**

**2015**

**1987**



* *une personne séropositive sous ART efficace ne transmet pas le VIH par contact sexuel (Déclaration Suisse, 2008)*

* *Tous les patients doivent être sous traitement*

**Comment (mieux) vivre sous ARVs?**

# Amélioration de l'efficacité au cours du temps

**77,999 subjects (**181 studies)

Principal backbones

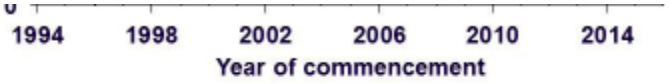
- TDF/TAF-FTC, 44.2%
- thymidine-based , 27.7%
- abacavir-lamivudine , 9.7%

Principal anchors

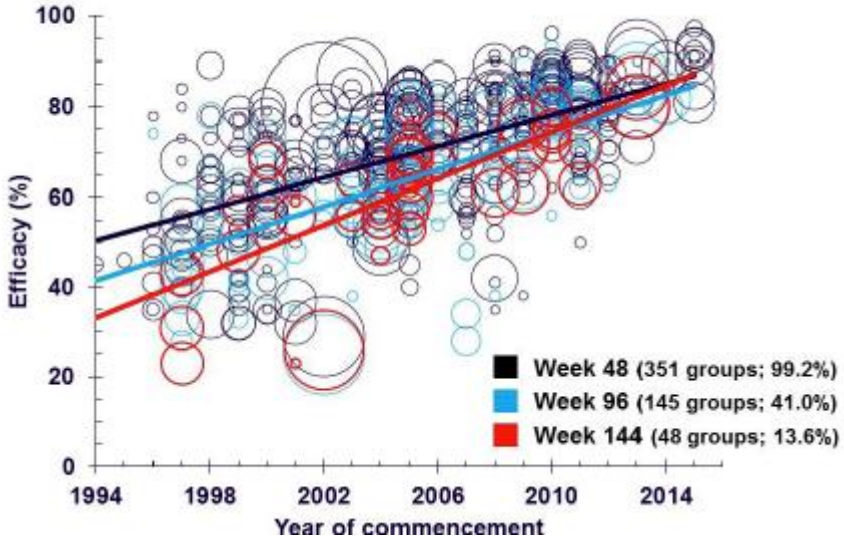
- NNRTI, 49.7%
- PI/r, 28.1%
- INSTI; 11.5%

Mean ITT efficacy (RNA<50 copies/mL) at W48, 96, 144

- 71.3%, 63.5% and 61.8%




| | | | | | |
|---|---|---|---|---|---|
| Wk 48 | 57.2% | 68.8% | 76.9% | 83.8% | p<0.001 |
| Wk 96 | 51.6% | 60.5% | 64.8% | 79.9% | p<0.001 |
| Wk 144 | 45.1% | 54.5% | 71.6% | 77.1% | p<0.001 |




Independent predictors of greater efficacy at Weeks 48, 96 and 144

- TDF/TAF-FTC and INSTI
- pre-ART R genotyping, higher baseline CD4 and once-daily ARV (W48)
- Fewer pills/day (Weeks 96 and 144)

Phase-4 studies yielded progressively < efficacy than phase-3 studies (-5.1% W48, -15.8% W144)

- Cessation through W144 : declined over time: overall (29.4%), adverse events (8.9%)
- no decline for virological failure (5.2%)

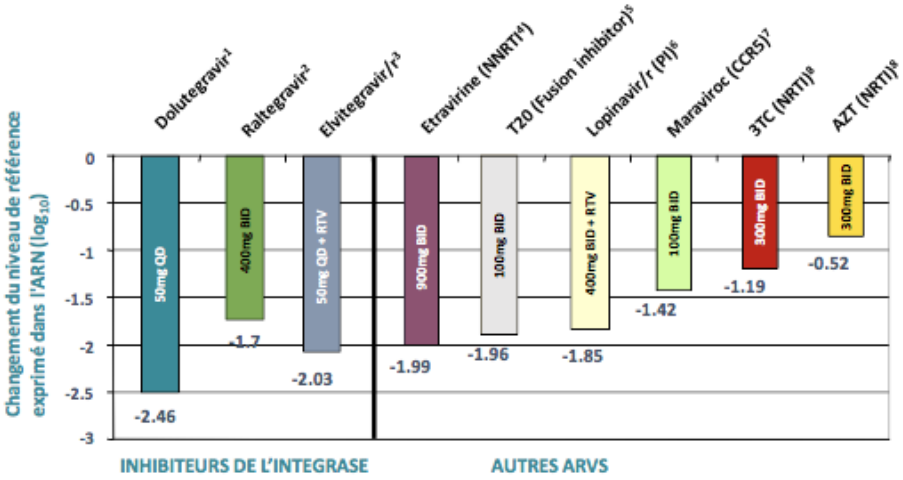
**Conclusions**

- Initial ART efficacy continues to improve **BUT >20% of post-2010 subjects failed over 3 years**
- Real-world efficacy is lower than in phase-3 trials.
- Guidelines should list non-INSTI-based initial ART as non-preferred.
- Strategies to improve access to pre-ART genotyping and to increase early initiation of OD ART.

# MEDICAMENTS

Devenus bien plus puissants depuis la commercialisation de l'AZT en 1987

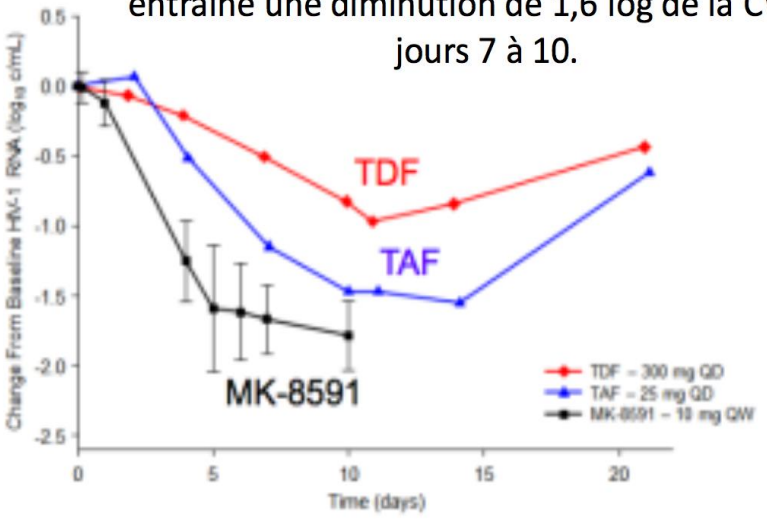
## Puissance: activité du médicament en monothérapie




## Exemple d'un nouveau nucléosidique NRTTI MK-8591: Inhibiteur de la translocation de la RT des nucléosides (EFdA)

MK-8591 (phase 1b):

Une seule dose orale de 10 mg une fois par semaine entraîne une diminution de 1,6 log de la CV aux jours 7 à 10.




*Friedman, et al., CROI 2016 Poster 437LB, Matthews RP et al, IAS 2017, abstract #* TUPDB0202 LB

# Combinaisons de médicaments à dose fixe (homologation FDA 2018)

générique seulement

2DR 21.11.2017

| NOMS COMMERCIAUX | ATRIPLA[1] | EVIPLERA[2] ODEFSEY[6] | STRIBILD[3] | TRIUMEQ[4] | GENVOYA[5] | SYMTUZA[7] (17.07.2018) | BIKTARVY[8] (07.02.2018) | DELSTRIGO[10] (30.08.2018) | TLD TAF-LD* | JULUCA[9] |
|---|---|---|---|---|---|---|---|---|---|---|
| COMPOSANTS (noms DCI) | Generic FDC TDF/XTC/EFV | TDF/FTC/RPV TAF/FTC/RPV | TDF/FTC/EVG/c | ABC/3TC/DTG | TAF/FTC/EVG/c | TAF/FTC/DRV/c | TAF/BIC/FTC | TDF/FTC/DOR | TDF/FTC/DTG | DTG/RPV |
| CONSIDERATIONS | Troubles neuro-psychiatriques | CV <100,000 | Interactions médicamenteuses | HLAB*5701 co-infection | médicaments–interactions | médicaments–interactions | Long-term data | Long-term data | TAF TB DTG grossess | Approval based on 48-weeks data from phase III SWORD 1-2 switch studies |

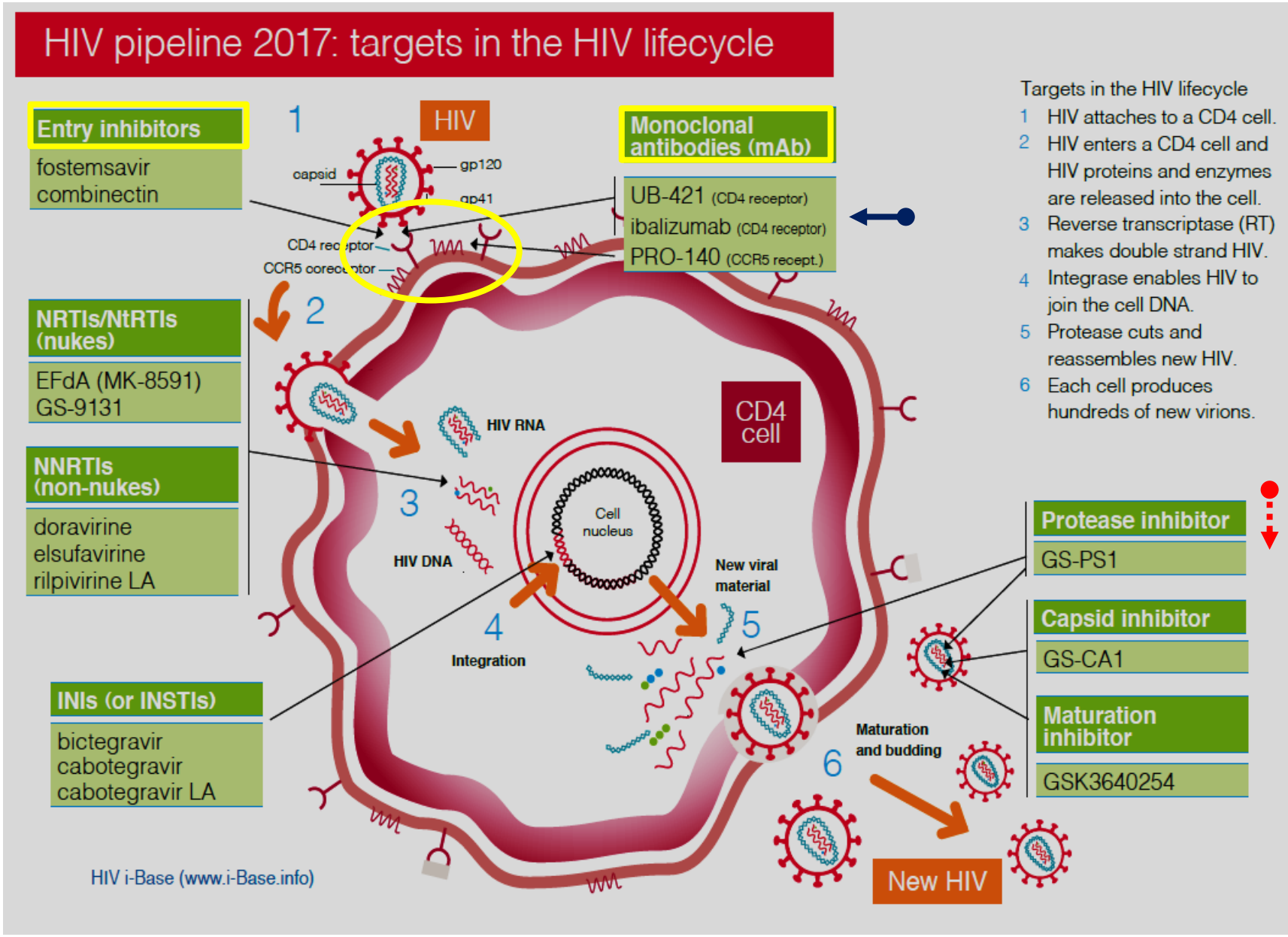
Combinaisons 1x/jour dose-fixe. Taille des comprimés non mis à l'échelle.

*JAMA, Saag et al, août 2018

*Courtesy of Chloé Orkin, CROI 2018 (with permission)*


1. Atripla SmPC. Available from: https://www.medicines.org.uk/emc/medicine/20505. Updated May 2017. Accessed October 2017;
2. Eviplera SmPC. Available from: https://www.medicines.org.uk/emc/medicine/25518. Updated June 2017. Accessed October 2017;
3. Stribild SmPC. Available from: https://www.medicines.org.uk/emc/medicine/27810. Updated June 2017. Accessed October 2017;
4. Triumeq SmPC. Available from: https://www.medicines.org.uk/emc/medicine/29178. Updated January 2017. Accessed October 2017;
5. Genvoya SmPC. Available from: https://www.medicines.org.uk/emc/medicine/31225. Updated September 2017. Accessed October 2017;
6. Odefsey SmPC. Available from: https://www.medicines.org.uk/emc/medicine/32117. Updated September 2017. Accessed October 2017;
7. Symtuza SmPC. Available from: http://www.medicines.org.uk/emc/medicine/34148. Updated September 2017. Accessed October 2017;
8. Biktarvy PI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf. Accessed February 2018;
9. Juluca SmPC. Available from: https://www.viivhealthcare.com/our-medicines/juluca.aspx. Updated November 2017. Accessed December 2017
10 Chloé Orkin et al, *Clinical Infectious Diseases*, ciy540, https://doi.org/10.1093/cid/ciy540.

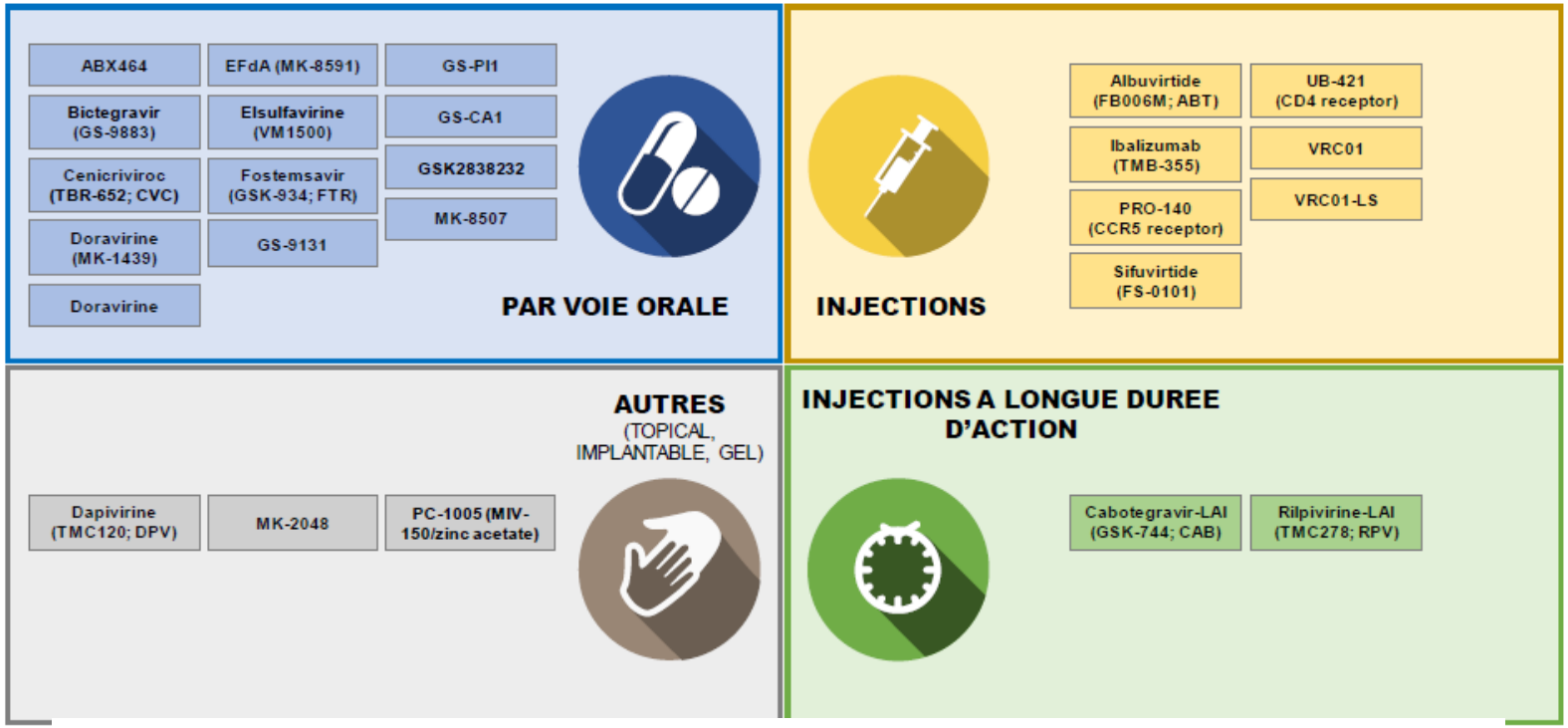
# HIV pipeline 2017: targets in the HIV lifecycle




Targets in the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
3. Reverse transcriptase (RT) makes double strand HIV.
4. Integrase enables HIV to join the cell DNA.
5. Protease cuts and reassembles new HIV.
6. Each cell produces hundreds of new virions.

# Comment administrer les traitements?




LED

## Cabotegravir, rilpivirine:

*Le pionnier des nouvelles voies d'administration*

*Nous avons le potentiel de révolutionner la manière de dispenser la thérapie ARV*

**Injections**
Ex. Formulation actuelle du cabotegravir et RIL

**Implants**
Ex. MK 8591, TAF

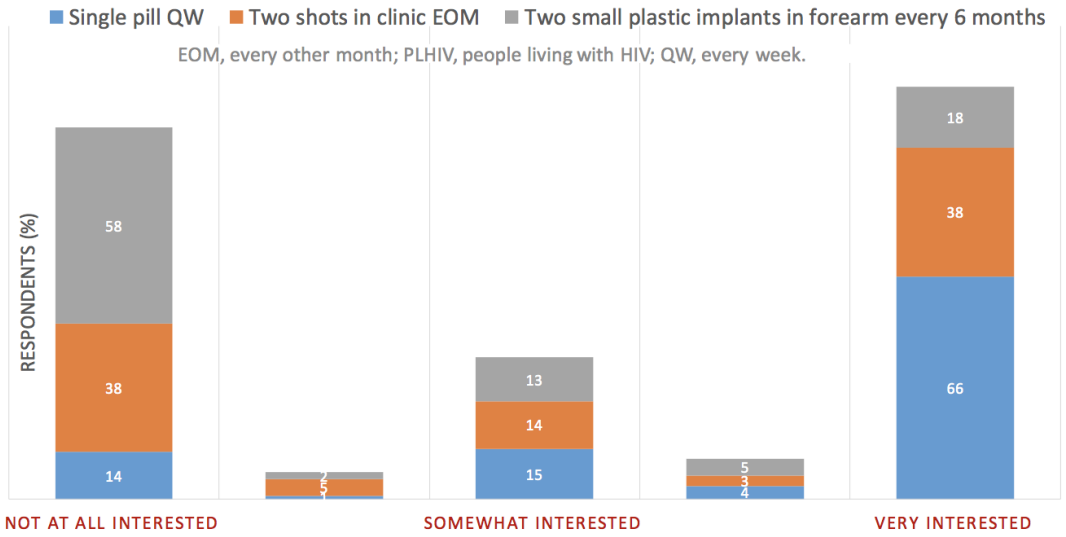
**Granules adaptées aux enfants**

**micro-needles**

**Anneau Vaginal**

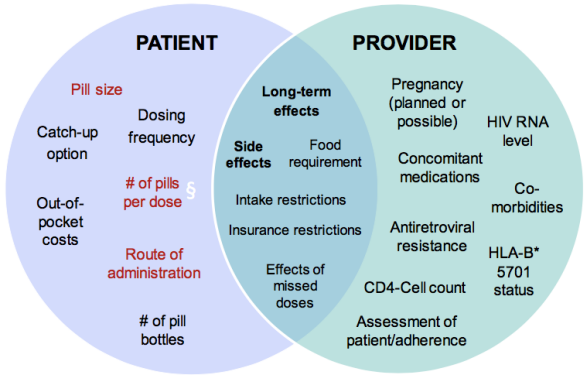
# Les patients sont-ils intéressés par ces nouveautés?

*Seriez vous intéressés à modifier votre traitements pour les options suivantes* *Osterman J, et al. CROI 2018, poster 503.*




# Quels sont les déterminants du traitement idéal?

*Comment optimiser le traitement?*




**What do people want? Variables influencing antiretroviral treatment selection[1]**

*Ylverton et al, AIDS PATIENT CARE and STDs Volume 32, Number 9, 2018*

# Injections à longue durée d'action

## Phase III molecules with new administration routes

*Cabotegravir-LA/rilpivirine-LA*

**Fostemsavir (BMS-663068)**
Prodrug of BMS-626529
Attachment inhibitor
*BMS → ViiV*

**Cabotegravir-LA (GSK-744; CAB)**
For PrEP
INI, *ViiV*

**Cabotegravir-LA + Rilpivirine-LA**
Maintenance strategy
*ViiV + Janssen*

- Cabotegravir-LA/rilpivirine-LA in a maintenance strategy have consistently presented encouraging long term data (week 160) *(Margolis et al, J Int AIDS Soc 2018, 21(S8):e25187, P118)*
- Good CNS penetration *(Letendre et al, J Int AIDS Soc 2018, 21(S8):e25187, 0346)* but some concerns:
  - the dosing volumes (3mls intra muscularly in the current formulation)
  - the need for oral lead
  - and the deliverability of injections that is resource-intensive (staff time, frequent visit clinics with dosing frequency every 1-2 months etc.)

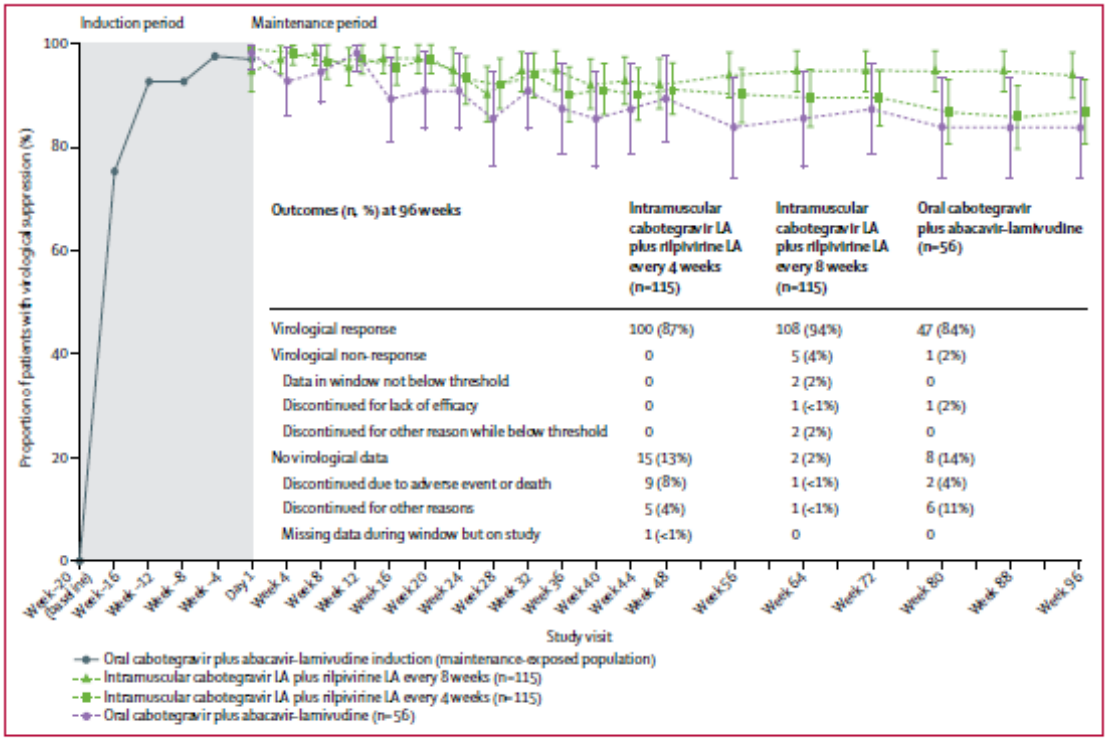
HIV Drug Therapy 2018

*Margolis et al, J Int AIDS Soc 2018, 21(S8):e25187, P118; Letendre et al, J Int AIDS Soc 2018, 21(S8):e25187, 0346*

# Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

David A Margolis, Juan Gonzalez-Garcia, Hans-Jürgen Stellbrink, Joseph J Eron, Yazdan Yazdanpanah, Daniel Podzamczer, Thomas Lutz,

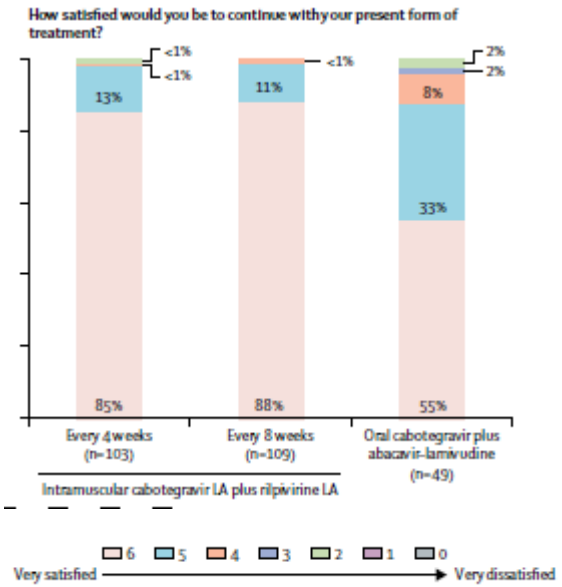
Lancet 2017



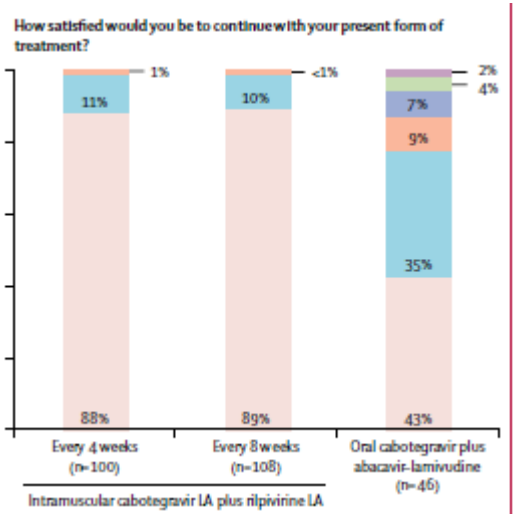

| Outcomes (n, %) at 96 weeks | Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115) | Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115) | Oral cabotegravir plus abacavir-lamivudine (n=56) |
|---|---|---|---|
| Virological response | 100 (87%) | 108 (94%) | 47 (84%) |
| Virological non-response | 0 | 5 (4%) | 1 (2%) |
| Data in window not below threshold | 0 | 2 (2%) | 0 |
| Discontinued for lack of efficacy | 0 | 1 (<1%) | 1 (2%) |
| Discontinued for other reason while below threshold | 0 | 2 (2%) | 0 |
| No virological data | 15 (13%) | 2 (2%) | 8 (14%) |
| Discontinued due to adverse event or death | 9 (8%) | 1 (<1%) | 2 (4%) |
| Discontinued for other reasons | 5 (4%) | 1 (<1%) | 6 (11%) |
| Missing data during window but on study | 1 (<1%) | 0 | 0 |

**Figure 2:** Proportion of patients with HIV-1 RNA concentration less than 50 copies per mL (FDA snapshot algorithm) by visit in the maintenance-exposed population and snapshot outcomes at week 96

**W48**




**W96**




The two-drug combination of all-injectable (IM), LA-cabotegravir+rilpivirine every 4 weeks or
8 weeks was as effective as daily 3-drug oral therapy at maintaining HIV-1 viral suppression through W96 and was well accepted and tolerated.

# Injection Ac Neutralisants : bNAbs anti-gp120

## contexte d'interruption thérapeutique

### A phase Ib trial

*Deux anticorps sont mieux qu'un seul*

**VRC family**[8] **(VRC01LS, VRC07, VRC07-523LS, 10E8VLS, N6LS …)**
bNAbs against gp120
For prevention or treatment
*NIH*

**10-1074(LS) + 3BNC117(LS)**[14]
bNAbs against gp120
For prevention or treatment
*Rockefeller; NIH*

**PGDM1400 + PGT121**
bNAbs against gp120
For prevention or treatment
*IAVI*

**GS-9722**[13]
bNAb against gp120
*Gilead*

**▪Phase Ib clinical trial (n=9)**

- Trois injections à 0,3 et 6 semaines de deux anticorps puissants, neutralisants en ciblant des sites indépendants situés sur l'enveloppe du VIH-1.

***La combinaison des anticorps monoclonaux Abs 3BCN117 et 10-1074 anti-VIH-1 maintient la suppression virale plusieurs semaines en l'absence de traitement antirétroviral***

*Mendoza P et al, Nature Research, 27 September 2018 (Vol 561)*

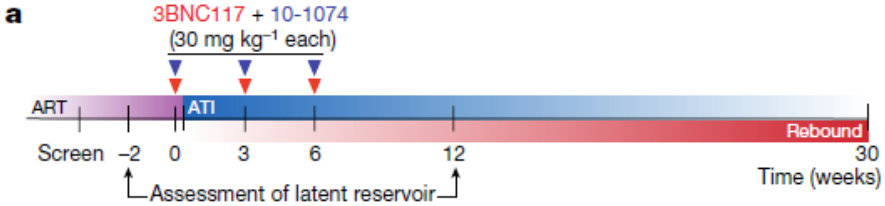
3BNC117 = bNAbs that target the CD4 binding site on the HIV-1 envelope spike
10-1074 = bNAb that targets the base of the V3 loop and surrounding glycans

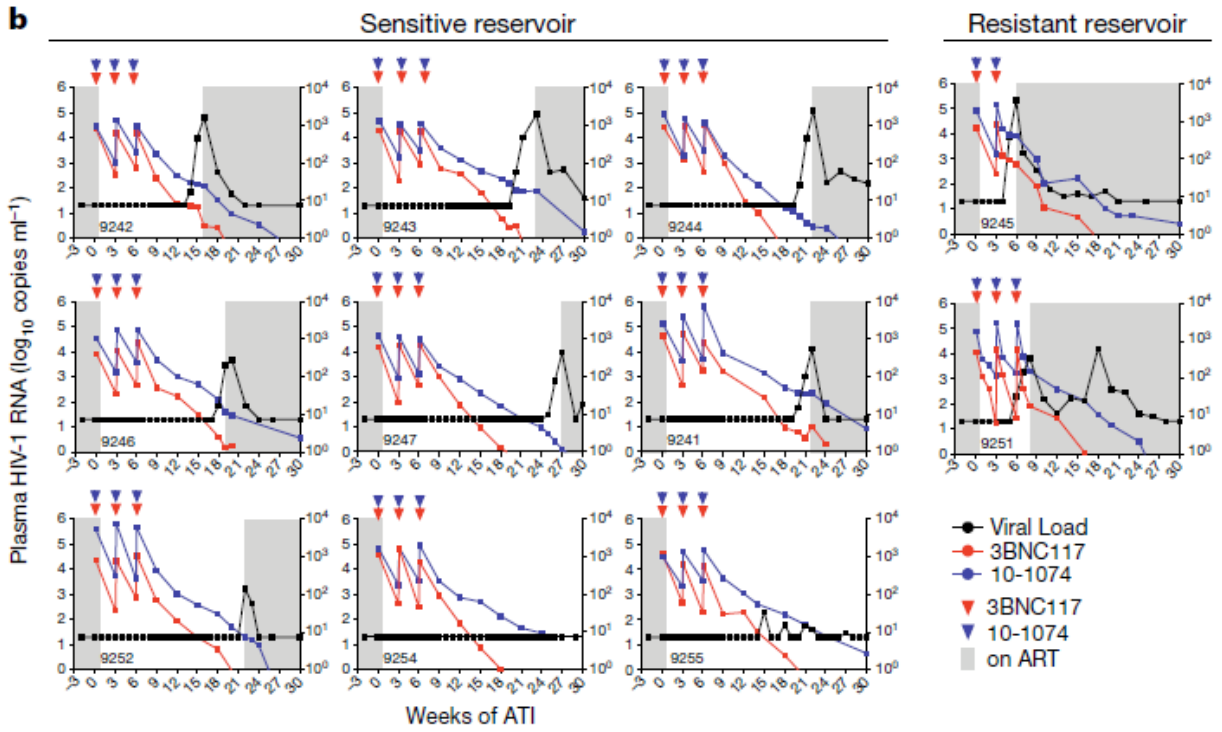
ARTICLE
https://doi.org/10.1038/s41586-018-0531-2

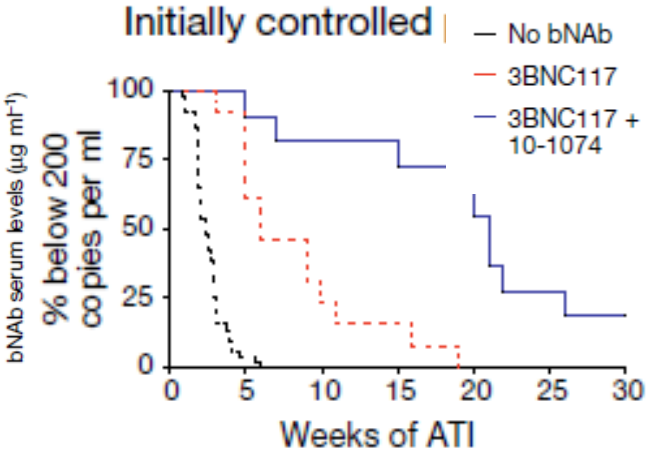
# Combination therapy with anti–HIV–1 antibodies maintains viral suppression

**Nature 2018**

Pilar Mendoza[1,19], Henning Gruell[2,3,4,19], Lilian Nogueira[1], Joy A. Pai[1], Allison L. Butler[1], Katrina Millard[1], Clara Lehmann[3,4,5],




A single administration of combinations of bNAbs with extended half-lives could maintain suppression for 6–12 months in individuals harbouring sensitive viruses

# Mr V, 48 ans

- Né en Guinée Bissau. A vécu à Lisbonne pendant 20 ans, retour en Guinée en 2010. Vit actuellement chez sa soeur. Pas d'intoxication alcoolo-tabagique. Pas de toxicomanie.
- Infection VIH-2  diagnostiquée  en octobre 2015 avec une Cryptococcose disséminée.
- CD4 à 40/$mm^3$ (Nadir) ; charge virale  VIH-2 à 6600 copies ; HLA B5701 négatif.
- Hospitalisation et traitement initial par ABC/3TC/DTG
- Prophylaxie par BACTRIM. Traitement par TRIFLUCAN.

- Échec viro-immunologique initial avec observance très douteuse.
- En Novembre 2016 CD4 à 144/$mm^3$

# Génotype en mars 2017

CV à 106 cp/ml; CD4 à 137/mm$^3$

**Nucleoside Reverse Transcriptase Inhibitors (NRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Epivir® / Emtriva® Lamivudine / Emtricitabine (3TC_FTC) | 184V | 3 | | R - Resistance |
| Ziagen® Abacavir (ABC) | 184V | 1 | | S - Susceptible |
| Zerit® Stavudine (D4T) * | | 3 | | R - Resistance |
| Videx® Didanosine (DDI) ** | | 3 | | R - Resistance |
| Viread® Tenofovir Alafenamide (TDF_TAF) | | 1 | | S - Susceptible |
| Retrovir® Zidovudine (ZDV) | | 1 | | S - Susceptible |

**Non-Nucleoside Reverse transcriptase Inhibitors (NNRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Doravirine (DOR) *** | | 3 | | R - Resistance |
| Sustiva®,Stocrin® Efavirenz (EFV) | | 3 | | R - Resistance |
| Intelence® Etravirine TMC125 (ETR) | | 3 | | R - Resistance |
| Viramune® Nevirapine (NVP) | | 3 | | R - Resistance |
| Rilpivirine (RPV) | | 3 | | R - Resistance |

**Integrase Strand Transfer Inhibitors (INSTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Bictegravir (BIC) | 92Q, 97A | 2 | | I - Possible resistance |
| Cabotegravir (CAB) | 92Q, 97A | 2 | | I - Possible resistance |
| Dolutegravir BID (DTG) | 92Q, 97A | 2 | | I - Possible resistance |
| Elvitegravir (EVG) | 92Q, 97A | 3 | | R - Resistance |
| Isentress® Raltegravir (RAL) | 92Q, 97A | 3 | | R - Resistance |

Que faites-vous ?

# Mr V, 48 ans

- Switch pour TDF + DRV 600/100 x 2.
- Observance catastrophique avec défaut de compréhension et mauvaise délivrance des médicaments par la pharmacie.
- Nouvel échec viro-immunologique.

# Génotype en novembre 2017

CV à 1735 cp/ml; CD4 à 137/mm$^3$

**Nucleoside Reverse Transcriptase Inhibitors (NRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Epivir® / Emtriva® Lamivudine / Emtricitabine (3TC_FTC) | 65R | 2 | | I - Possible resistance |
| Ziagen® Abacavir (ABC) | 65R | 3 | | R - Resistance |
| Zerit® Stavudine (D4T) * | | 3 | | R - Resistance |
| Videx® Didanosine (DDI) ** | | 3 | | R - Resistance |
| Viread® Tenofovir Alafenamide (TDF_TAF) | 65R, 111I | 3 | | R - Resistance |
| Retrovir® Zidovudine (ZDV) | 65R | 1 | | S - Susceptible |

**Non-Nucleoside Reverse transcriptase Inhibitors (NNRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Doravirine (DOR) *** | | 3 | | R - Resistance |
| Sustiva®,Stocrin® Efavirenz (EFV) | | 3 | | R - Resistance |
| Intelence® Etravirine TMC125 (ETR) | | 3 | | R - Resistance |
| Viramune® Nevirapine (NVP) | | 3 | | R - Resistance |
| Rilpivirine (RPV) | | 3 | | R - Resistance |

Echec de l'amplification de la protéase
Tropisme X4

Que faites-vous ?

# Mr V, 48 ans

- Sélection de la K65R d'où résistance au Ténofovir (protéase jamais amplifiable).
- En février 2018, switch pour AZT+LPV+DTG en 2 fois par jour
- Pas de contrôle de la réplication virale.

Que faites-vous ?

# Génotype en juillet 2018

CV à 442 cp/ml; CD4 à 104/mm$^3$

**Nucleoside Reverse Transcriptase Inhibitors (NRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Epivir® / Emtriva® Lamivudine / Emtricitabine (3TC_FTC) | | 1 | | S - Susceptible |
| Ziagen® Abacavir (ABC) | | 1 | | S - Susceptible |
| Zerit® Stavudine (D4T) * | | 3 | | R - Resistance |
| Videx® Didanosine (DDI) ** | | 3 | | R - Resistance |
| Viread® Tenofovir Alafenamide (TDF_TAF) | **111I** | 1 | | S - Susceptible |
| Retrovir® Zidovudine (ZDV) | | 1 | | S - Susceptible |

**Non-Nucleoside Reverse transcriptase Inhibitors (NNRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Doravirine (DOR) *** | | 3 | | R - Resistance |
| Sustiva®,Stocrin® Efavirenz (EFV) | | 3 | | R - Resistance |
| Intelence® Etravirine TMC125 (ETR) | | 3 | | R - Resistance |
| Viramune® Nevirapine (NVP) | | 3 | | R - Resistance |
| Rilpivirine (RPV) | | 3 | | R - Resistance |

**Integrase Strand Transfer Inhibitors (INSTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Bictegravir (BIC) | **92Q, 97A** | 2 | | I - Possible resistance |
| Cabotegravir (CAB) | **92Q, 97A** | 2 | | I - Possible resistance |
| Dolutegravir BID (DTG) | **92Q, 97A** | 2 | | I - Possible resistance |
| Elvitegravir (EVG) | **92Q, 97A** | 3 | | R - Resistance |
| Isentress® Raltegravir (RAL) | **92Q, 97A** | 3 | | R - Resistance |

**Attachment Inhibitors (AI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Fostemsavir (FTR) | | 3 | | R - Resistance |

# Génotype en octobre 2018

CV à 431 cp/ml

**Nucleoside Reverse Transcriptase Inhibitors (NRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Epivir® / Emtriva® Lamivudine / Emtricitabine (3TC_FTC) | 65R | 2 | | I - Possible resistance |
| Ziagen® Abacavir (ABC) | 65R | 3 | | R - Resistance |
| Zerit® Stavudine (D4T) * | | 3 | | R - Resistance |
| Videx® Didanosine (DDI) ** | | 3 | | R - Resistance |
| Viread® Tenofovir Alafenamide (TDF_TAF) | 65R | 3 | | R - Resistance |
| Retrovir® Zidovudine (ZDV) | **65R, 69S** | 1 | | S - Susceptible |

**Non-Nucleoside Reverse transcriptase Inhibitors (NNRTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Doravirine (DOR) *** | | 3 | | R - Resistance |
| Sustiva®,Stocrin® Efavirenz (EFV) | | 3 | | R - Resistance |
| Intelence® Etravirine TMC125 (ETR) | | 3 | | R - Resistance |
| Viramune® Nevirapine (NVP) | | 3 | | R - Resistance |
| Rilpivirine (RPV) | | 3 | | R - Resistance |

**Integrase Strand Transfer Inhibitors (INSTI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Bictegravir (BIC) | 92Q, 97A, 155H | 3 | | R - Resistance |
| Cabotegravir (CAB) | 92Q, 97A, 155H | 3 | | R - Resistance |
| Dolutegravir BID (DTG) | 92Q, 97A, 155H | 3 | | R - Resistance |
| Elvitegravir (EVG) | 92Q, **97A**, 155H | 3 | | R - Resistance |
| Isentress® Raltegravir (RAL) | 92Q, 97A, 155H | 3 | | R - Resistance |

**Attachment Inhibitors (AI2)**

| Drug | Mutations list | Range | Color | Interpretation |
|---|---|---|---|---|
| Fostemsavir (FTR) | | 3 | | R - Resistance |

- Hospitalisation le 23/10 et mise sous : Foscarnet 6 gx2/j et AZT+3TC +ATV/r +DRV 600x2+DTG 50x2.
- Charge virale de contrôle du 30/10 et 16/11 : négatives. CD4 à 122/$mm^3$(10 %).
- Pas de syndrome de restauration immunitaire. Attente du bictegravir en relais.
- Le 19/11 obtention du bictegravir et donc arrêt du Foscarnet, du Dolutégravir et du Reyataz et instauration du TAF/FTC/BIC en poursuivant AZT/3TC/DRV/r
- En raison des toxicités rénales et hépatique, arrêt des différents traitements pour wash out le 26/11 et transfert à Tenon pour PBR qui met en évidence une néphropathie chronique non étiquetée et aggravée par le foscarnet.

- Reprise le 15 décembre par AZT/DRV/r + Foscarnet (initialement 6g x2 pendant 5 jours puis 6 g 1j/2 pour protéger le rein), sans anti-intégrase car N155H apparue sur le génotypage prélevé avant la mise sous bictégravir.
- Négativation de la charge virale en 10 jours.
- Puis repositivation autour de 350 copies. Passage de nouveau à Foscarnet 6g x 2/j.
- ATU demandée pour ibalizumab et EFdA.

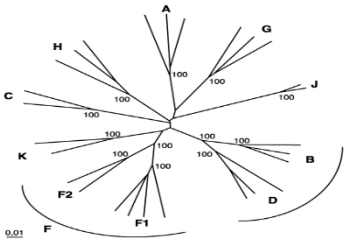
# Diversité génétique actuelle

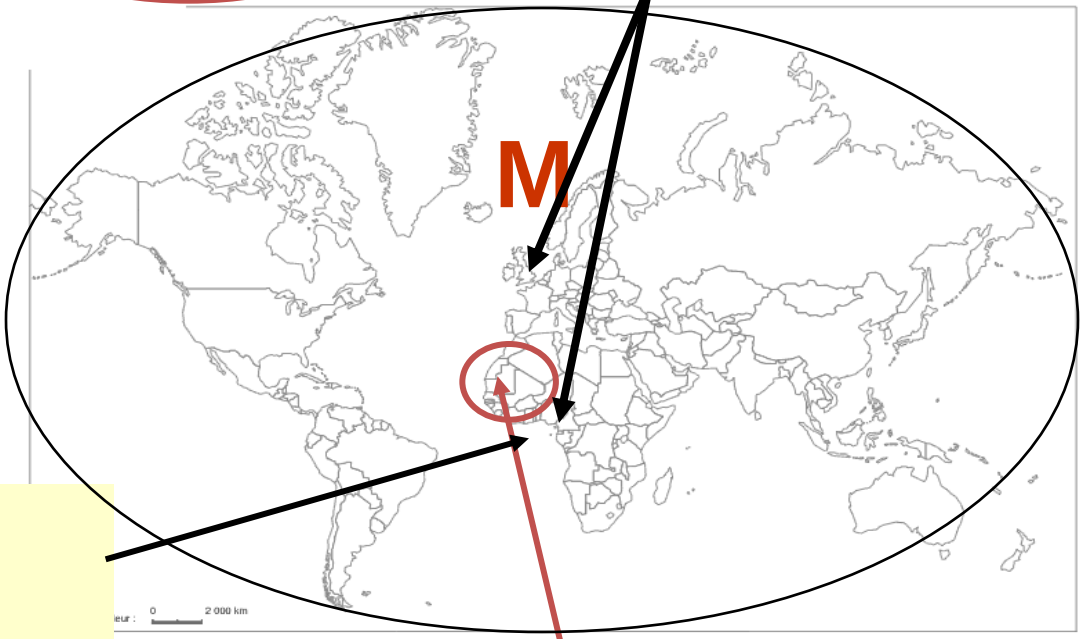
***2 types***

**Groupe P**

**VIH-1 groupe M *(major)***

- **sous-types et CRFs** (Circulating Recombinant Form) **(recombinants « épidémiques »)**




**VIH-1** **groupe O *(outlier)***

**groupe N *(non-M/non-O)***

**VIH-2 : 8 groupes A-H**

Conséquences **physiopathologiques, épidémiologiques**, **diagnostiques**, **thérapeutiques** & **vaccinales**

# VIH-2

| | VIH-1 | VIH-2 |
|---|---|---|
| Mode de transmission, cibles cellulaire, mode de réplication | Pas de différence | |
| Génome | | Homologie sur l'enveloppe de 40% |
| Prévalence en France | 93,9% des infections | 0,4% des infections (0,6% de coinfections) |
| Progression de l'infection | Perte de 49 CD4/an | Perte de 9 CD4/an<br>Plus lente vers le Sida |
| Sensibilité aux ARV | A toutes les classes | Résistance au INNTI (Doravirine), T-20<br>Diminution de la sensibilité à certains IP, Fostemsavir |

# Activité du Foscarnet sur le virus du VIH

- Analogue pyrophosphate: Inhibe la synthèse et bloque l'activité de la DNA polymérase ainsi que celle de la reverse transcriptase

- In vitro: synergie entre le Foscarnet et les analogues de la thymidine

- Efficacité sur le VIH-1: ↓ CV de 1,15 à 2,1 log10

# Bictegravir
# Données virologiques

## INTEGRASE INHIBITORS & MUTATIONS : Index de résistance *in vitro*

| Single Primary Mutations | | | | |
|---|---|---|---|---|
| IN Genotype | Fold Change vs WT | | | |
| | BIC | DTG | EVG | RAL |
| T66I | 0.3 | 0.4 | 15 | 1.1 |
| T66A | 0.4 | 0.4 | 11 | 1.2 |
| T66K | 1.4 | 2.1 | 50 | 9.8 |
| E92Q | 1.2 | 1.4 | 29 | 4.9 |
| E92G | 1.3 | 1.7 | 16 | 2.1 |
| T97A | 0.6 | 0.6 | 3.8 | 1.6 |
| F121Y | 0.4 | 0.6 | 16 | 5.3 |

| Single Primary Mutations | | | | |
|---|---|---|---|---|
| IN Genotype | Fold Change vs WT | | | |
| | BIC | DTG | EVG | RAL |
| Y143R | 1.3 | 1.2 | 3.4 | 16.0 |
| Y143H | 0.9 | 1.1 | 1.6 | 2.5 |
| Y143C | 0.9 | 0.9 | 2.2 | 4.3 |
| S147G | 1.0 | 1.0 | 5.8 | 1.3 |
| Q148R | 0.7 | 0.6 | 109 | 28 |
| Q148H | 0.7 | 0.8 | 8.7 | 4.3 |
| Q148K | 0.9 | 0.6 | 119 | 41 |
| N155H | 1.3 | 1.4 | 44 | 13 |
| R263K | 1.7 | 1.7 | 4.5 | 1.2 |

$EC_{50}$ Fold Change (FC) vs Reference Wild Type

| < 2.5 BIC<br>< 4.0 DTG<br>< 2.5 EVG<br>< 1.5 RAL | 2.5 to < 10 BIC<br>4.0 to < 13 DTG | ≥ 10 BIC<br>≥ 13 DTG<br>≥ 2.5 EVG<br>≥ 1.5 RAL |
|---|---|---|

Margot et al.; Submitted

# Bictegravir
# Données virologiques

## INTEGRASE INHIBITORS & MUTATIONS : Index de résistance *in vitro*

| G140A/C/S + Q148H/R/K +/- other | | |
|---|---|---|
| IN Genotype | Fold Change vs WT | |
| | DTG | BIC |
| G140S,Q148H | 3.44 | 2.12 |
| G140S,Q148H | 3.52 | 2.03 |
| G140S,Q148H | 3.59 | 2.42 |
| G140S,Q148H | 3.60 | 1.99 |
| G140S,Q148H | 4.00 | 2.17 |
| E138K,G140S,Q148H | 4.73 | 2.46 |
| G140S,Q148H | 5.56 | 2.49 |

| G140A/C/S + Q148H/R/K +/- other | | |
|---|---|---|
| IN Genotype | Fold Change vs WT | |
| | DTG | BIC |
| E138K,G140S,Q148H | 5.34 | 2.52 |
| G140S,Q148H | 5.46 | 2.92 |
| G140S,Q148R | 6.15 | 3.01 |
| E138K,G140C,Q148R | 8.58 | 5.32 |
| L74L/M,G140A,Q148R | 8.81 | 5.38 |
| L74M,G140C,Q148R | 9.06 | 8.36 |
| L74L/M,G140A,Q148R | 8.81 | 5.38 |
| L74M,G140C,Q148R | 9.06 | 8.36 |
| E138A, G140S,Q148H | 10 | 7.23 |
| G140S,Q148H | 11 | 3.81 |

| G140A/C/S + Q148H/R/K +/- other | | |
|---|---|---|
| IN Genotype | Fold Change vs WT | |
| | DTG | BIC |
| E138K,G140S,Q148H | 13 | 2.62 |
| G140S,Q148H | 13 | 4.37 |
| T97A,G140S,Q148H | 14 | 7.62 |
| T97A,G140S,Q148H | 15 | 4.39 |
| G140S,Q148R | 17 | 7.05 |
| E138K,G140A,Q148K | 63 | 19 |

- **BIC has an improved resistance profile compared to DTG (p=0.037)**

$EC_{50}$ Fold Change (FC) vs Reference Wild Type

| < 2.5 BIC<br>< 4.0 DTG<br>< 2.5 EVG<br>< 1.5 RAL | 2.5 to < 10 BIC<br>4.0 to < 13 DTG | ≥ 10 BIC<br>≥ 13 DTG<br>≥ 2.5 EVG<br>≥ 1.5 RAL |
|---|---|---|

White K, et al., European Workshop HIV & Hep 2016. Rome, Italy. Poster O-01. Tsiang M, et al., AAC 2016;60:7086-7097.

# Sélection de résistance in vitro avec les INI : BIC vs DTG

- **Expériences de pression de sélection à partir de virus porteurs de mutations aux INI :** E92Q, Q148R, R263K, N155H

## Profils génotypiques et phénotypiques des virus sélectionnés in vitro après passages multiples

| Virus J0 | Mutations intégrase sélectionnées par BIC | FC BIC | FC DTG | CR | Mutations intégrase sélectionnées par DTG | FC BIC | FC DTG | CR |
|---|---|---|---|---|---|---|---|---|
| E92Q | E92Q-G140G/E-M154M/I | 0,9 | 1,7 | 2 % | E92Q | 1,1 | 1,4 | 13 % |
| Q148R | Q148R | 0,6 | 0,6 | 4,9 % | G52G/E-E138K-Q148R-H171H/Y | 1,4 | 1,4 | 3,5 % |
| R263K | R263K | 1,7 | 1,6 | NR | R263K | 1,6 | 1,8 | 7,5 % |
| N155H | L45Q-N155H | 1,5 | 1,5 | 59 % | S147N-N155H | NR | NR | NR |

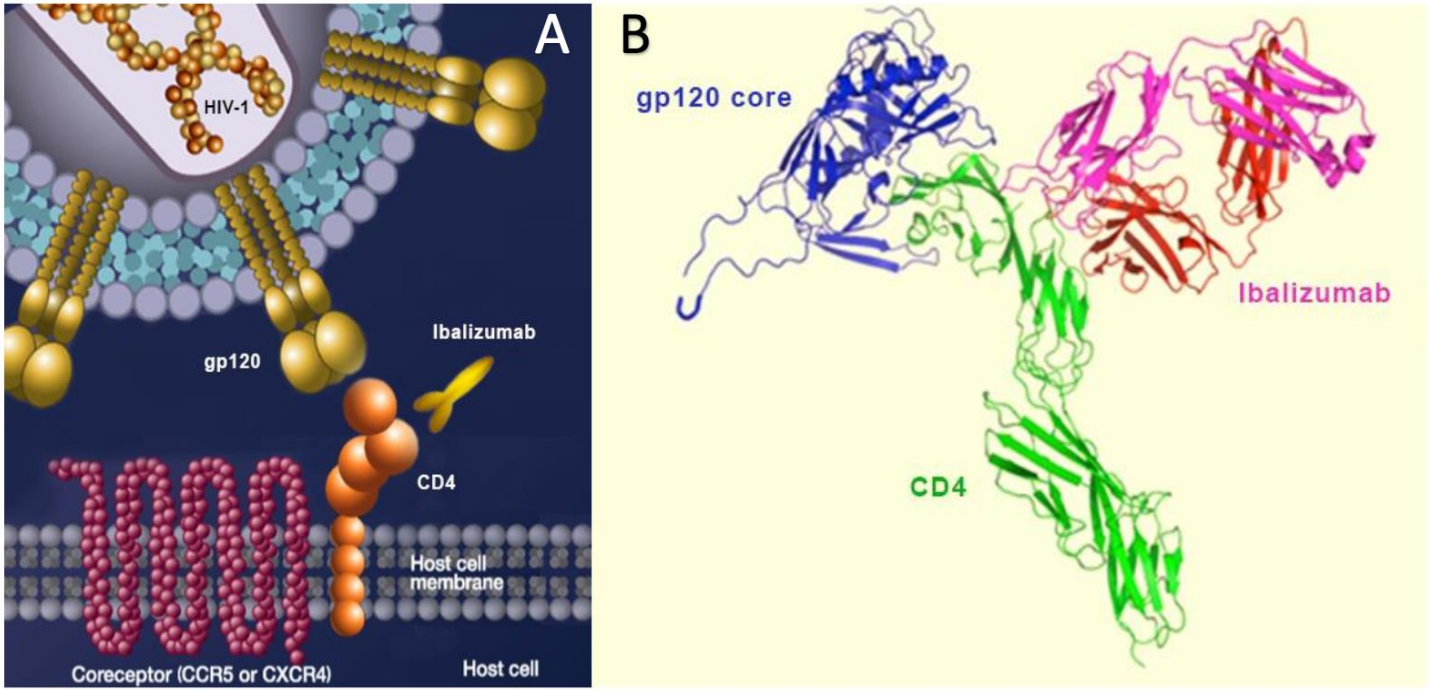
CR : capacité réplicative virale, NR : non réalisé

- Mutant E92Q-G140E : FC BIC > 100, FC DTG > 200 et CR < 1 %

- **Conclusions**
  - Identification de 2 profils de résistance à BIC : S153F/Y (FC < 2) et E92Q-G140E (FC > 100 mais CR < 1 % → non présent in vivo ?)
  - L'ensemble des virus sélectionnés sous pression d'INI reste sensible à BIC ou avec une faible ↗ du FC

*Andreatta K, CROI 2018, Abs. 546*

# Ibalizumab: Ac monoclonal qui bloque l'entrée en se liant au CD4 de manière non compétitive




A. Ibalizumab blocks HIV-1 from infecting CD4+ T-cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.

B. Ibalizumab mAb structure resolved by X-ray crystallography and epitope mapping, demonstrating distinct binding site to gp120 binding site on CD4.

# Ibalizumab FDA Approved as Salvage Therapy

- **Ibalizumab**: humanized mAb to CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells[1]

| Key US Label Information[1] | |
|---|---|
| Indication | ▪ For heavily treatment–experienced patients with multidrug-resistant HIV who are experiencing failure of current ART; for use in combination with other ARVs |
| Dosing | ▪ IV delivery; loading dose of 2000 mg followed by maintenance dose of 800 mg Q2W |

- **TMB-301/-311**: single-arm, open-label phase III trial in which patients resistant to ≥ 1 ARV from 3 classes but sensitive to ≥ 1 ARV with HIV-1 RNA > 1000 c/mL on current ART were treated with loading dose of ibalizumab + current ART for 2 wks followed by maintenance dose of ibalizumab Q2W + OBR (N = 40)[2-4]

| Virologic Outcome | Day 14[2] (N = 40) | Wk 24[3] (N = 40) | Wk 48[4] (N = 27) |
|---|---|---|---|
| ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease, % | 83* | NR | NR |
| Mean $\log_{10}$ HIV-1 RNA decrease | 1.1 | 1.6 | NR |
| HIV-1 RNA < 50 copies/mL, % | NR | 43 | 59 |
| HIV-1 RNA < 200 copies/mL, % | NR | 50 | 63 |

*Primary endpoint; $P < .0001$ vs 3% at end of control period.

1. Ibalizumab [package insert]. May 2018. 2. Lalezari J, et al. IDWeek 2016. Abstract LB-6.
3. Lewis S, et al. CROI 2017. Abstract 449LB. 4. Emu B, et al. IDWeek 2017. Abstract 1686.

# Ibaluzimab for MDR viruses

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

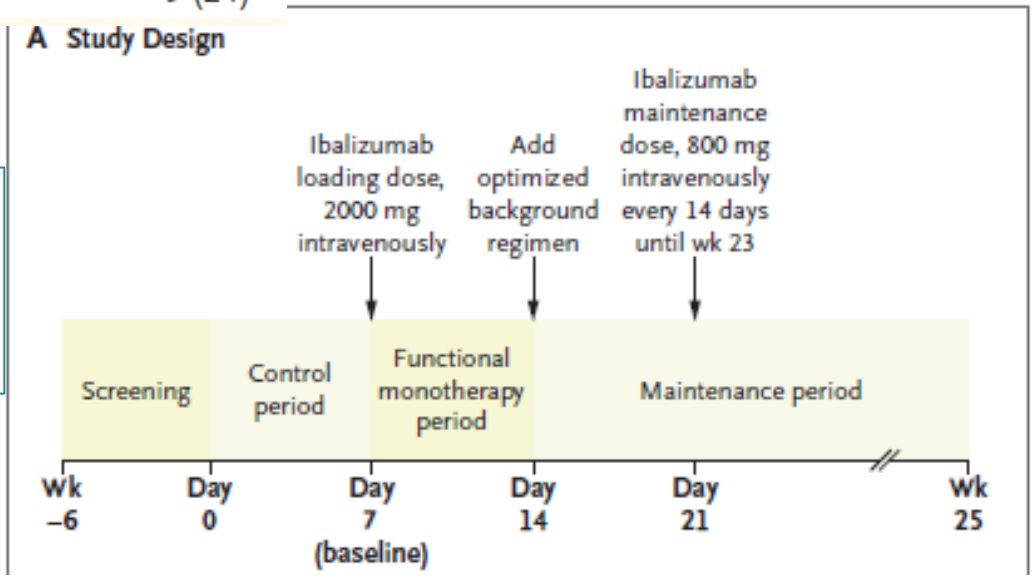
Brinda Emu, M.D., Jeffrey Fessel, M.D., Shannon Schrader, M.D., Princy Kumar, M.D., Gary Richmond, M.D., Sandra Win, M.D., Steven Weinheimer, Ph.D., Christian Marsolais, Ph.D., and Stanley Lewis, M.D.

- New treatments are needed for MDR HIV-1 infection.
- Ibalizumab = IgG4 monoclonal antibody that blocks HIV-1 entry by noncompetitively binding CD4, antiviral activity against MDR HIV-1.

| Known resistance to ≥1 drug in class — no. (%) | |
|---|---|
| Nucleoside reverse-transcriptase inhibitor | 37 (93) |
| Non-nucleoside reverse-transcriptase inhibitor | 37 (93) |
| Protease inhibitor | 36 (90) |
| Integrase inhibitor | 27 (68) |
| Coreceptor antagonist‡ | 33 (87) |
| Fusion inhibitor‡ | 9 (24) |

**31** patients completed the study.

- Mean baseline VL = **4.5** log10 c/ml
- Mean CD4 count = **150** /µl



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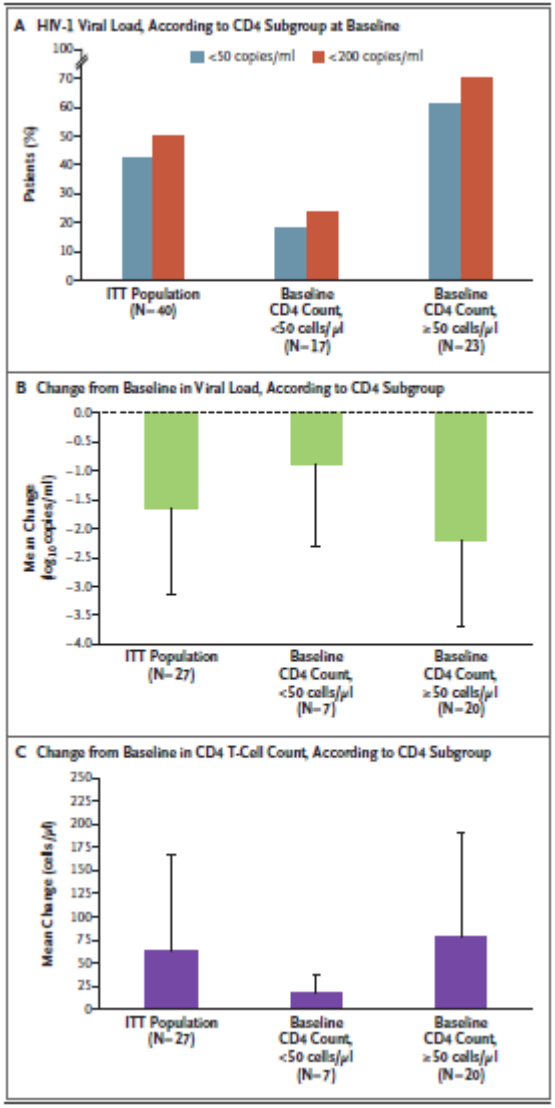
W25: ibalizumab + optimized background

- **mean decrease of 1.6 log 10 c/ml** from BL
- **43%** of the patients had a VL< **50 c/ml**
- **50%** had a VL<**200 c/ml**

In patients with MDR HIV, advanced disease, limited treatment options: ibalizumab had significant antiviral activity during a 25-week study

Emergence of diminished ibalizumab susceptibility observed in vitro in patients who had virologic failure.




Emu B et al. N Engl J Med 2018;379:645-654

# Ibalizumab Phase 3 extension

- 40 patients *(NEJM 2018 ; 379 : 645-54)*
  - Baseline CD4 = 73/$mm^3$
  - In 43% , need to use fostemsavir (no active ARV available)
  - Add-on Single infusion of IBA
    - Mean VL reduction at D7 : 1.1 $\log_{10}$ c/mL
  - From D14 : continuation of IBA (1 infusion every 2 weeks) + OBT
  - VL < 50 c/mL at W24 = 43%
- Roll-over (continuation) in 27/40 patients for 24 additional weeks
  - VL < 50 c/mL = 59% (including all suppressed at W24)
- Favorable safety profile
  - No infusion-related adverse events
  - Diarrhea, Dizziness, Nausea and Rash : ≥ 5%
  - 2 Severe adverse reactions
    - 1 rash
    - 1 IRIS

*Emu B. HIV Glasgow 2018; Glasgow, UK. Oral 345*

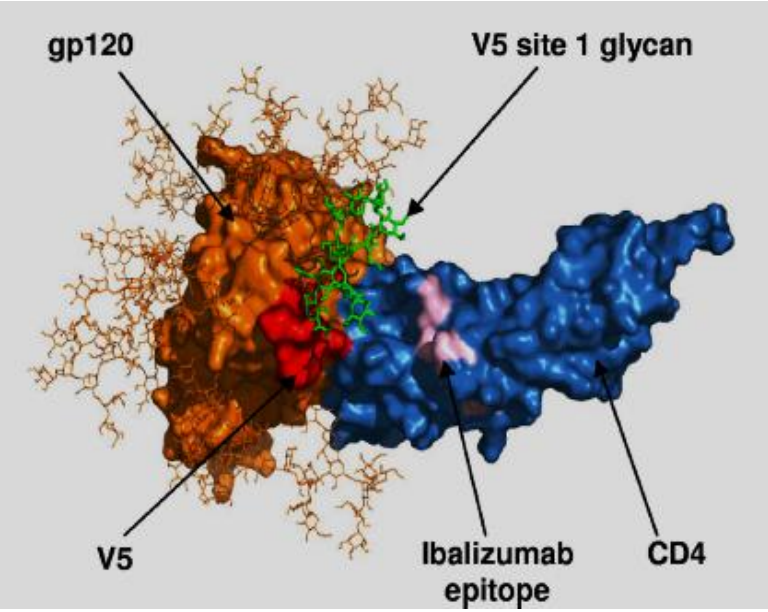
Loss of Asparagine-Linked Glycosylation Sites in Variable Region 5 of Human Immunodeficiency Virus Type 1 Envelope Is Associated with Resistance to CD4 Antibody Ibalizumab[▽]

*J.Toma et al ; J.Virol. 2011*

## Virologic failure or rebound

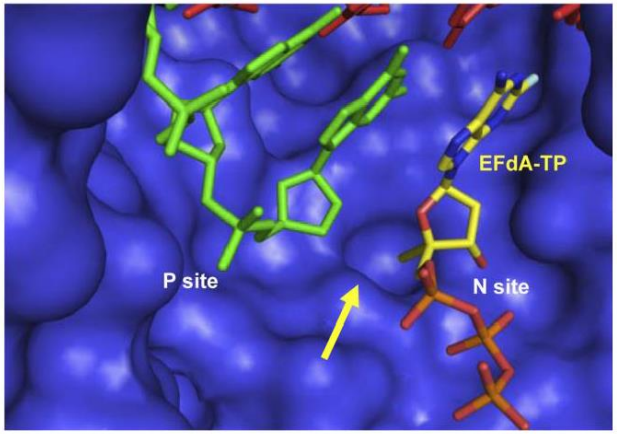
- lower degree of susceptibility to ibalizumab than at baseline (% inhibition in vitro)
- Loss of N-linked glycosylation sites in the V5 loop of HIV-1 gp120
- Ability of ibalizumab-resistant variants to facilitate CD4-induced conformational changes in the CD4-gp120 complex, which enable coreceptor engagement despite bound ibalizumab

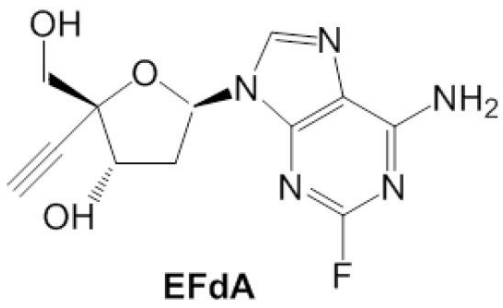
*B.Emu et al ; NEJM 2018*




V5 glycans are situated in **close proximity** to the gp120- CD4 interface.

# MK-8591 (EFdA): A Novel Nucleoside with a Unique Mechanism of Action




EFdA

- MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA) licensed from Yamasa
- Virologic profile and mechanism of action is extensively described in the literature (Mitsuya, Sarafianos, Parniak)
  - Non-obligate chain terminator
  - Inhibits reverse transcriptase by preventing translocation
  - Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad subtype and mutant coverage (HIV-1, HIV-2, MDR strains)

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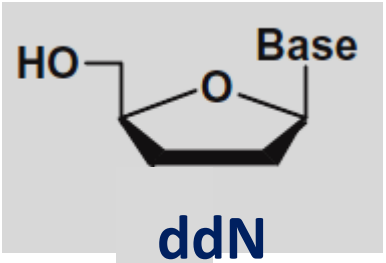
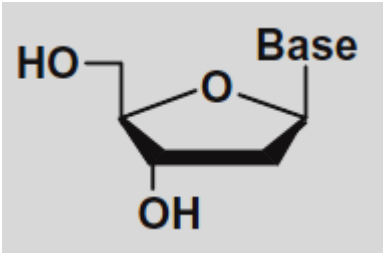
Michailidis et al. (2009) JBC




**ddN**

HIV discriminate



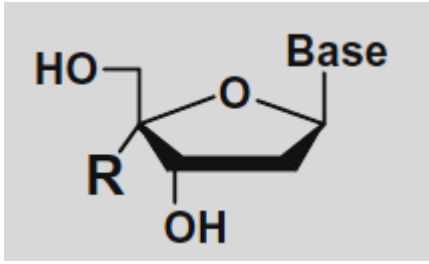

**dN**

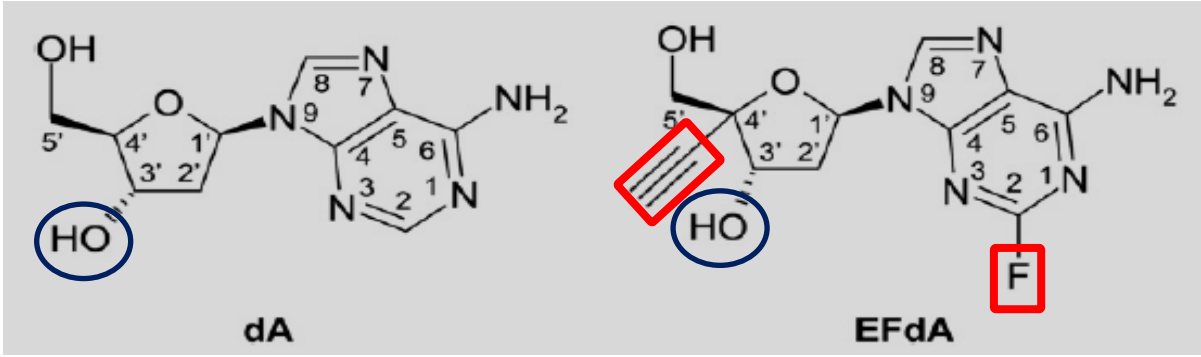
*These **EdN analogs**, unlike the existing approved nucleoside reverse transcriptase inhibitors, **possess a 3'-OH** in their sugar moiety; however, they **cause viral DNA chain termination**, resulting in RT inhibition*

***E.I Kodama et al ; AAC 2001***

HIV

cannot discriminate




4'-ethynyl-2-fluoro-2'- deoxyadenosine (**EFdA**; MK-8591)

# MK-8591: Resistance Profile

| | MK-8591 | Zidovudine | Tenofovir | Lamivudine |
|---|---|---|---|---|
| M184I (n = 5) | 3.9 ± 0.4 | 0.37 ± 0.04 | 0.58 ± 0.03 | >123 |
| M184V (n = 5) | 5.0 ± 0.9 | 0.44 ± 0.21 | 0.60 ± 0.11 | >79 |
| K65R (n = 7) | 0.16 ± 0.04 | 0.39 ± 0.14 | 1.7 ± 0.4 | 11 ± 7 |
| K65R + M184I/V (n = 7) | 2.1 ± 0.3 | 0.42 ± 0.22 | 1.3 ± 0.3 | > 69 |
| L74V (n = 3) | 0.21 ± 0.07 | 0.38 ± 0.10 | 0.54 ± 0.08 | 1.6 ± 0.6 |
| L74V + M184V (n = 2) | 2.3 ± 0.4 | 0.20 ± 0.05 | 0.37 ± 0.11 | > 69 |
| Q151M (n = 5) | 0.25 ± 0.11 | 84 ± 78 | 1.9 ± 0.8 | 11 ± 8 |
| Q151M + M184I/V (n = 6) | 3.1 ± 2.5 | 71 ± 95 | 1.1 ± 0.5 | > 69 |
| 3 TAMs + L74V (n = 4) | 1.2 ± 0.4 | 12 ± 11 | 1.4 ± 0.5 | 4.1 ± 1.6 |
| 3TAMs + M184I/V (n = 8) | 11 ± 5 | 34 ± 54 | 1.6 ± 0.7 | > 69 |

- MK-8591 and TFV pro-drugs have complementary resistance profiles
  - MK-8591 hyperactive against K65R / TFV hyperactive against M184 mutants
- TAMs confer low level resistance (< 4-fold) to MK-8591
  - M184I/V resistance is additive with TAMs

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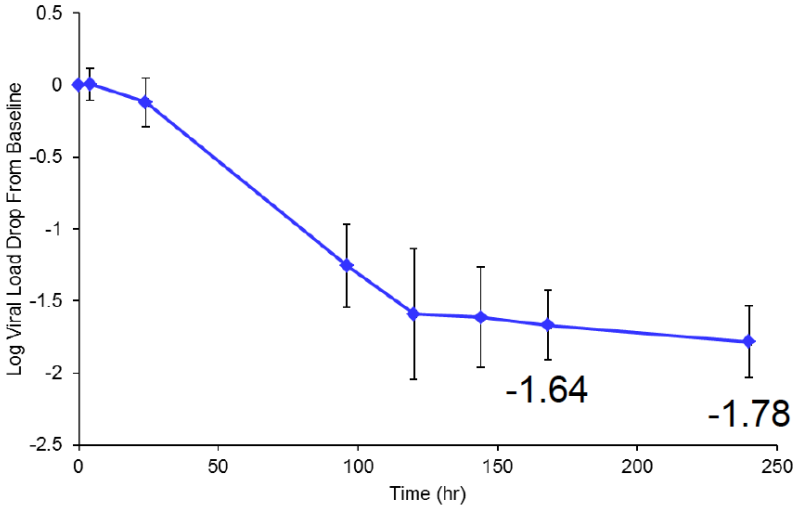
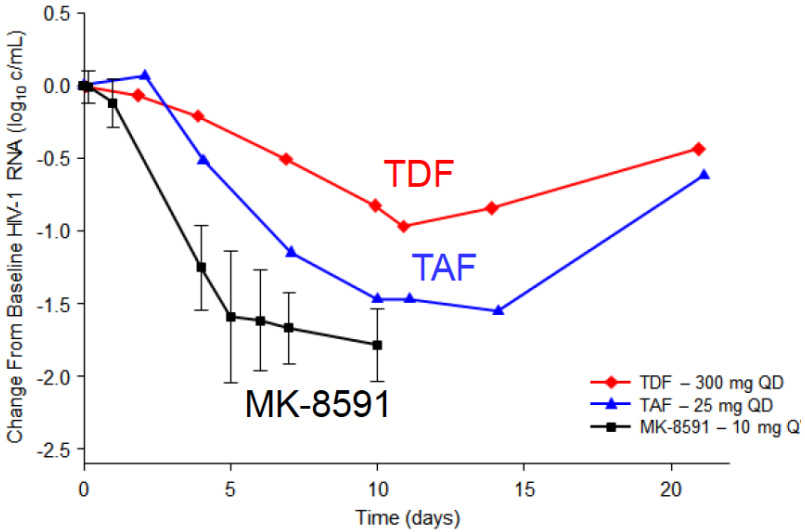
# MK-8591 is Effective in HIV patients when Dosed Once-Weekly: Results from ongoing Ph1b study




- A single 10 mg oral dose in HIV-infected patients results in ~1.6 log decrease in viral load at days 7-10
- Intracellular MK-8591-TP $t_{1/2}$ = 103 hr
- No evidence of resistance out to Day 10
- Greater rate and extent of initial viral load decline with a single MK-8591 dose than with QD TAF or TDF


Friedman et al. (2016) CROI
Ruane PJ, DeJesus E, Berger D, et al. (2013) JAIDS

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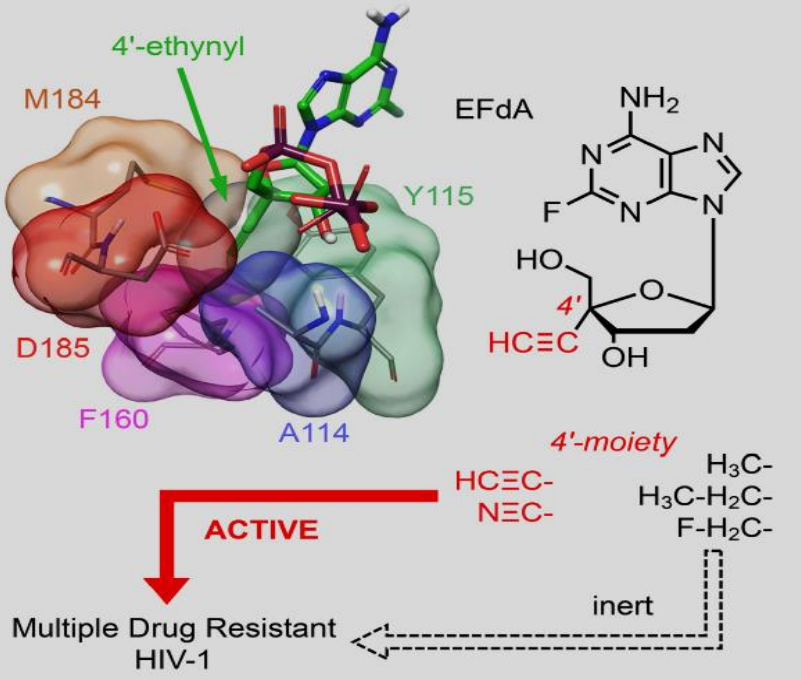
## M184I/V substitutions and E138K/M184I/V double substitutions in HIV reverse transcriptase do not significantly affect the antiviral activity of EFdA

*M.Oliveira et al ; JAC 2017*

## The High Genetic Barrier of EFdA/MK-8591 Stems from Strong Interactions with the Active Site of Drug-Resistant HIV-1 Reverse Transcriptase

*Y.Takamatsu et al ; Cell.Chem.Biol. 2018*




This activity was due to the **strong** van der Waals interactions with critical amino acid residues **A114, Y115, F160, and M184** present in the hydrophobic pocket of HIV-1 reverse transcriptase

**F160** is one of the most critical amino acids for HIV-1 RT activity, and thus the virus does not select F160 as a drug-resistant substitution. This strong vdW interaction was **not reduced** or lost even in the presence of drug-resistant mutations, such as **M184V**

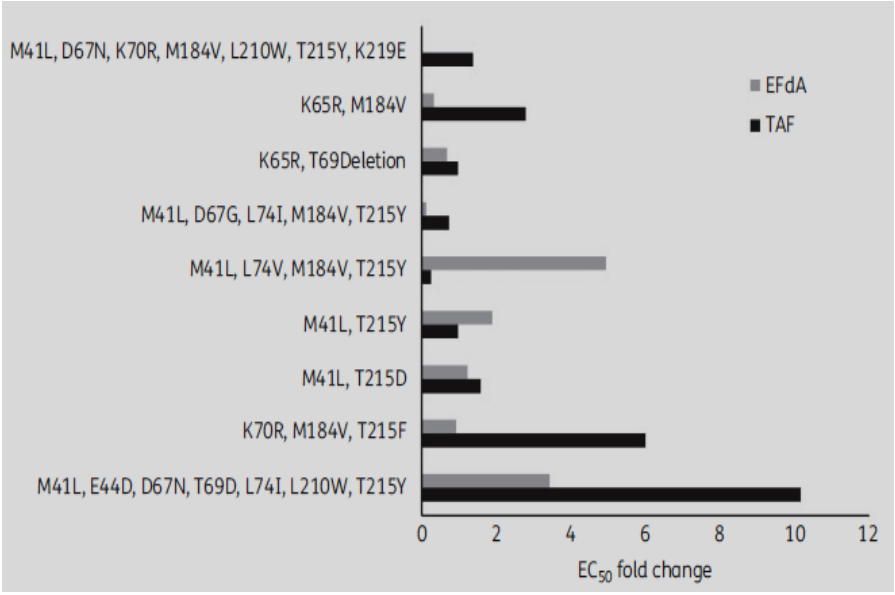
# Hypersusceptibility mechanism of Tenofovir-resistant HIV to EFdA

*E.Michailidis et al ; Retrovirology 2013*

**K65R RT**… a **significant decrease in the excision efficiency of EFdA-MP** from the 3’ primer terminus appears to be the primary cause of increased susceptibility to the inhibitor

## Antiretroviral potency of 4′-ethnyl-2′-fluoro-2′-deoxyadenosine, tenofovir alafenamide and second-generation NNRTIs across diverse HIV-1 subtypes

*D.T Njenda et al ; JAC 2018*




EFdA consistently suppressed both therapy-naive and resistant viruses. The **K65R**- and **M184V**-carrying strains were suppressed more effectively by EFdA than by tenofovir alafenamide