

# Uzun Etkili ART

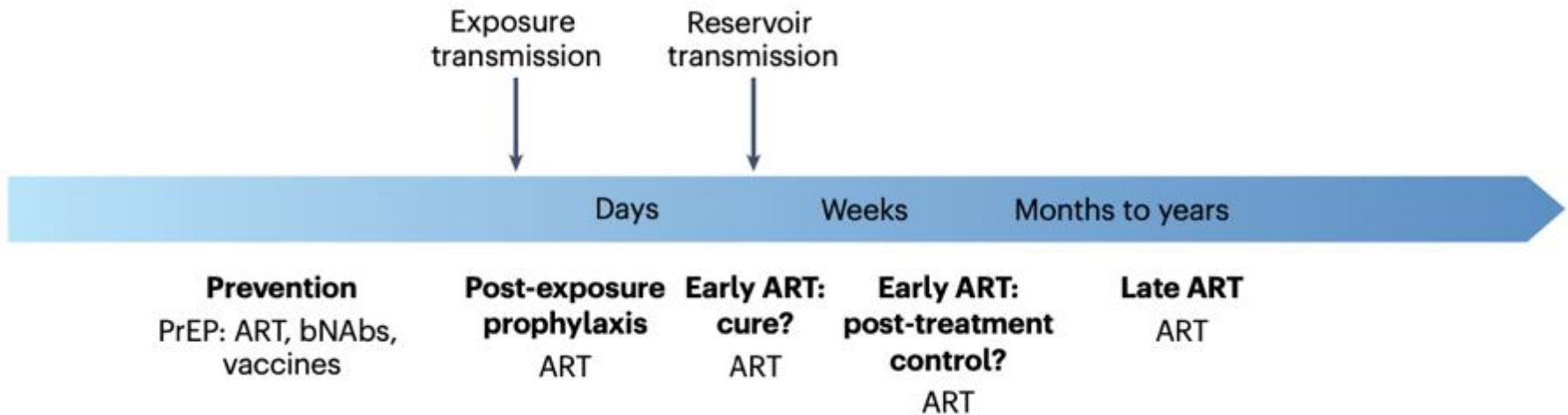
Ahmet Çağkan İnkaya  
Hacettepe Üniversitesi Tıp Fakültesi  
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inkaya@hacettepe.edu.tr



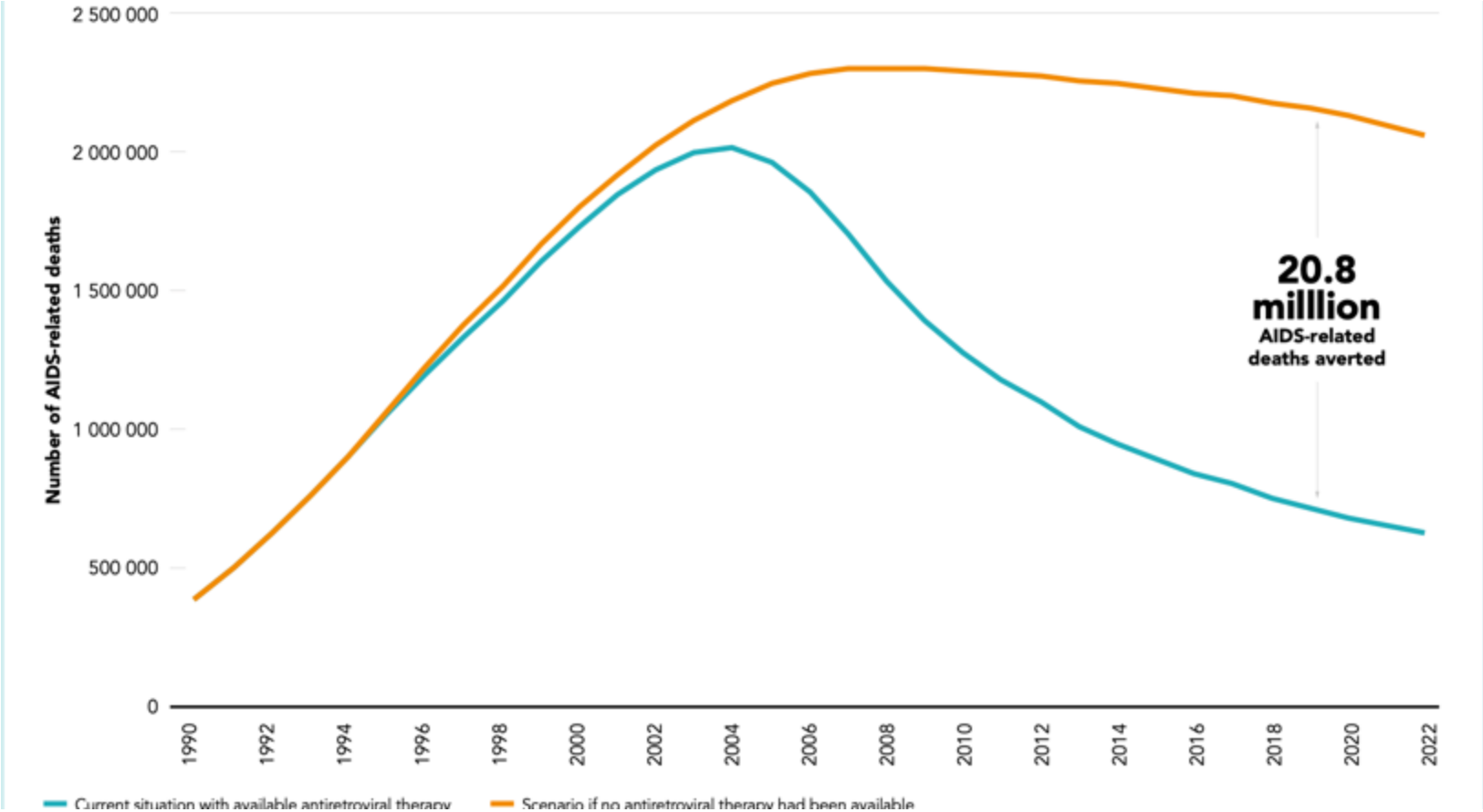
# Çıkar Çatışması

- Konuşma: GSK-ViiV, Gilead, MSD
- Advisor Board: GSK-ViiV, Gilead, MSD
- Klinik Araştırma: MSD
- Bilimsel Proje: Hacettepe BAP, TÜSEB, TÜBİTAK

# HIV Yönetimi: Çok Şey Öğrendik



# Kurtarılan Hayatlar

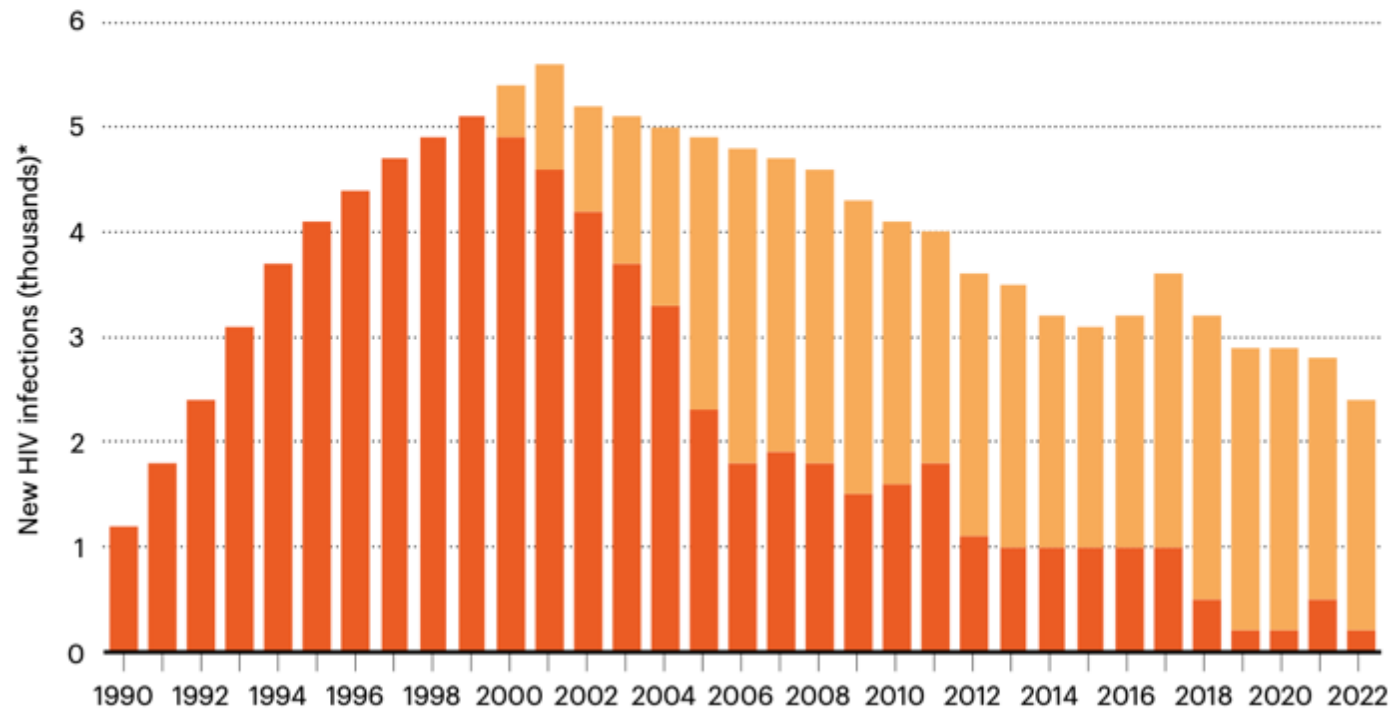


# Annenen Bebeęe Geçiřin Engellenmesi

## BUILDING ON SUCCESS

Botswana has achieved an impressive reduction in the rate of parent-to-child transmission of HIV, but more needs to be done to reach certain communities.

- New HIV infections in children (0–14)
- New infections averted owing to prevention of parent-to-child transmission



\*These data are point estimates within a possible range. For complete data on the upper and lower bounds of these estimates, refer to [aidsinfo.unaids.org](https://aidsinfo.unaids.org).

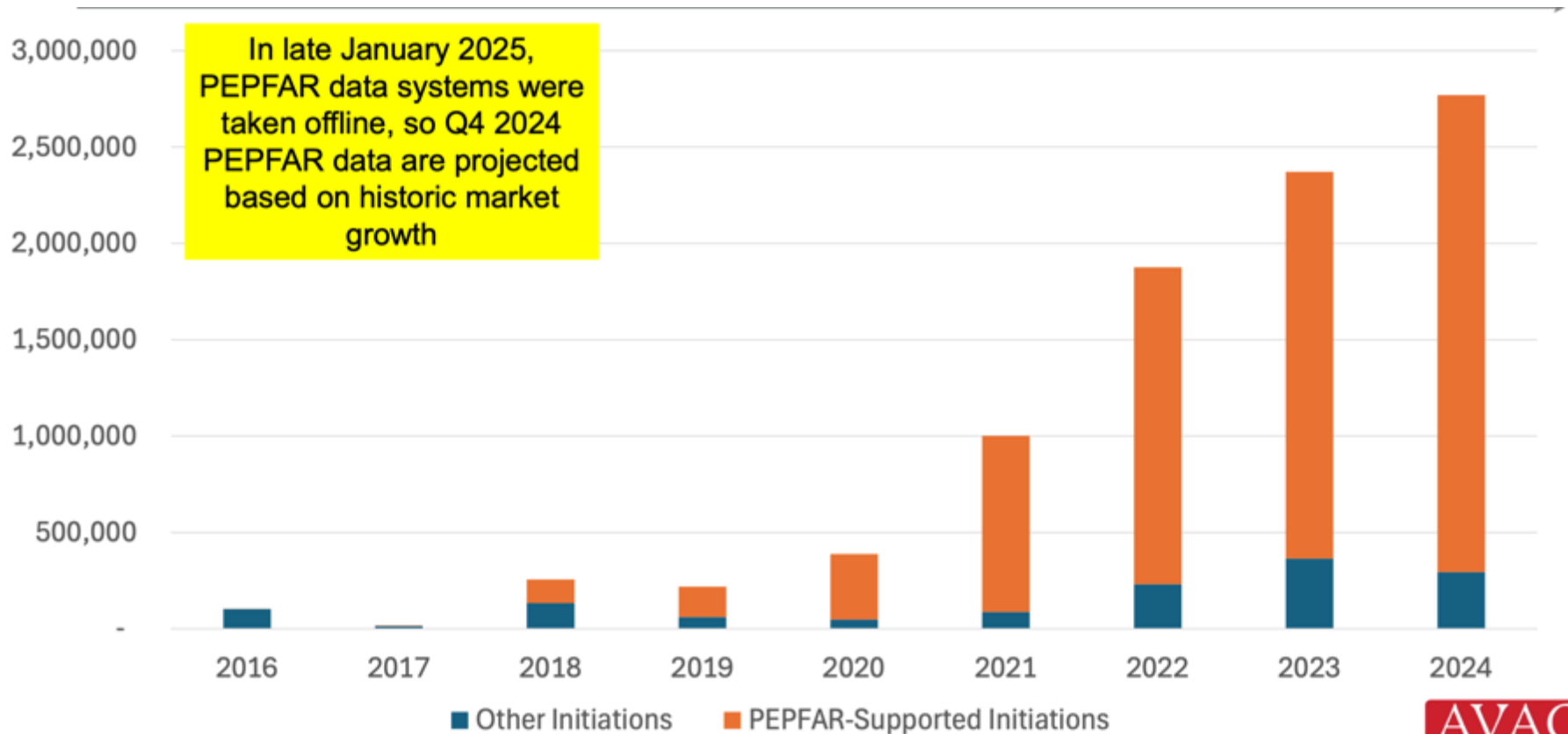
# Belirlenemeyen Bulaştırmayan

**U=U**

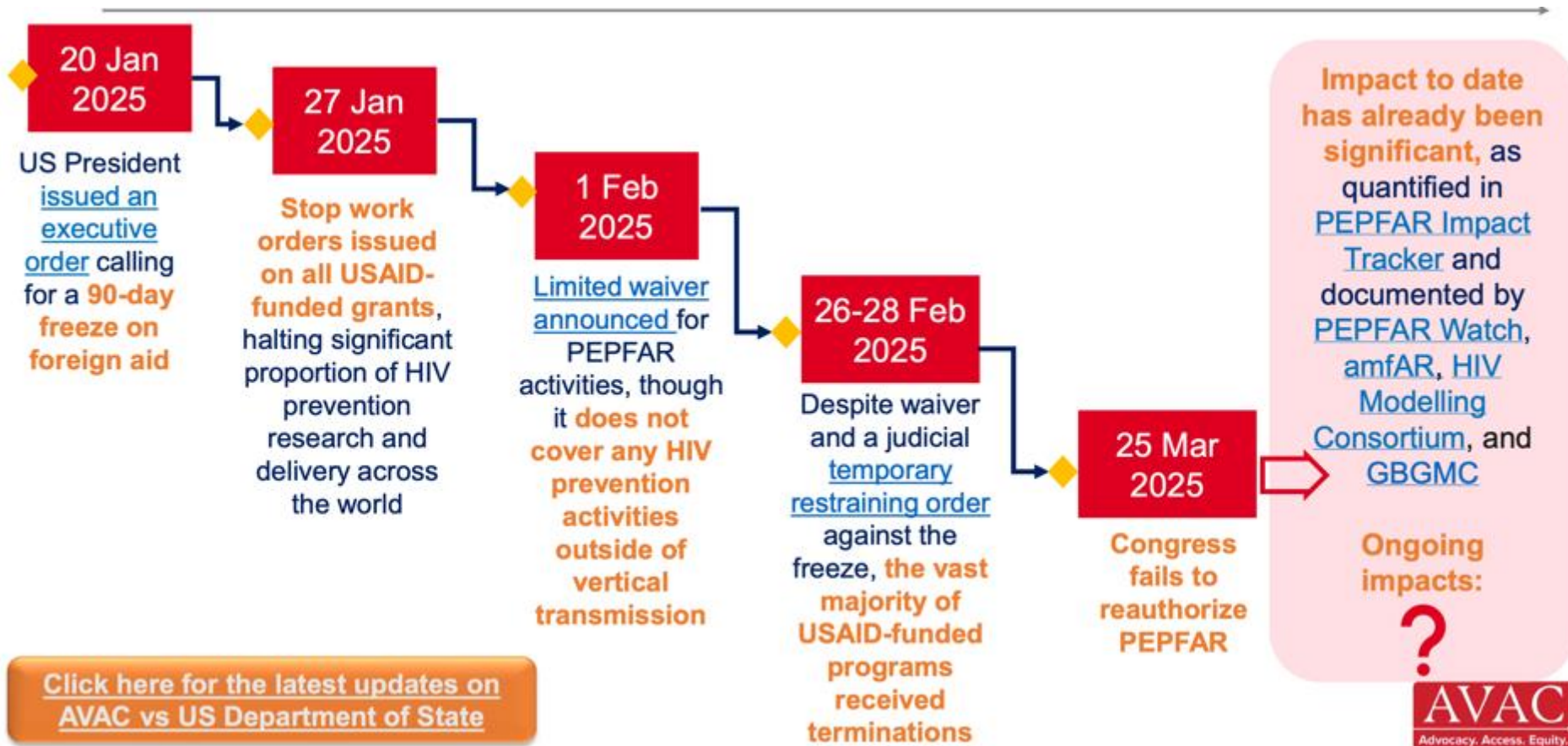
**undetectable = untransmittable**



# PEPFAR: Kuruluş 2003

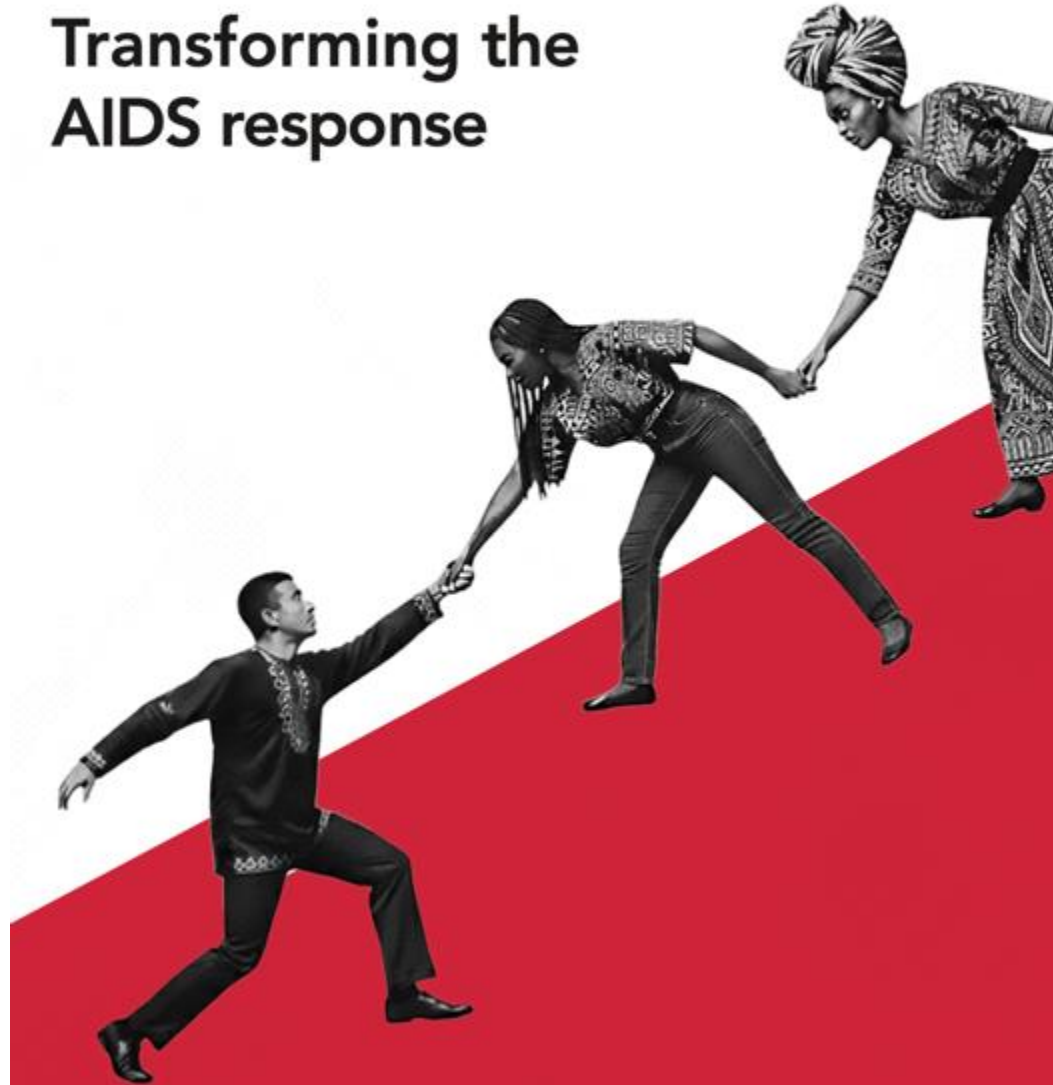


# PEPFAR: Yıkımın Hikayesi



# OVERCOMING DISRUPTION

Transforming the  
AIDS response



WORLD AIDS DAY | 2025

# ABD Artık Dünya AIDS Gününde Anma Programı Düzenlemeyecek

☰ **CNN Health** Life, But Better Fitness Food Sleep Mindfulness Relationships

## The US government is no longer commemorating World AIDS Day

DEC 2, 2025 ▾

By  [Jennifer Hansler](#)



World AIDS Day has been marked every December 1 since 1988. (Debarchan Chatterjee/NurPhoto/AP)

# Ne vereyim Asuman'a?

Günde tek tabl?

İki ayda bir im?

Haftada 1 tabl?

6 ayda 1 sc?

Aylık iğne

Antikor  
kombo?

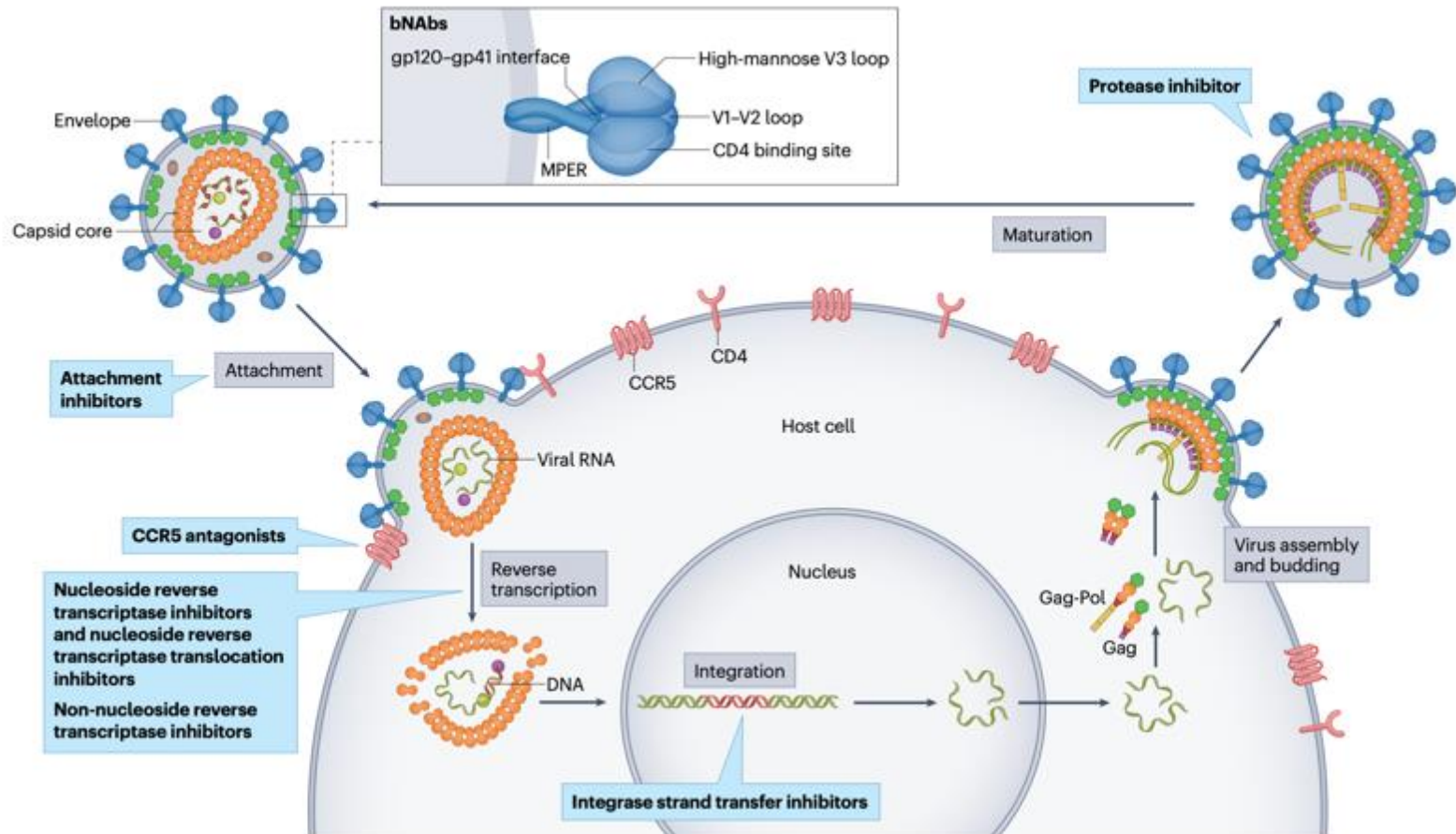
Implant?



# ART'de Karşılanmamış İhtiyaçlar

- İlaç yorgunluğu
- Uyum sorunu yaşayan kişiler
- Stigma
- Ayrımcılık
- Daha az klinik visit
- Daha iyi maliyet
- Kullanıcı memnuniyeti

# HIV Viroloji



# Uzun Etkili ARV: İlk Çalışmalar

European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 502–508



Contents lists available at ScienceDirect  
European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: [www.elsevier.com/locate/ejpb](http://www.elsevier.com/locate/ejpb)



Research paper

## Development of a long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment

Lieven Baert<sup>a,\*</sup>, Gerben van 't Klooster<sup>a</sup>, Willy Dries<sup>b</sup>, Marc François<sup>b</sup>, Alfons Wouters<sup>b</sup>, Esther Bastanie<sup>b</sup>, Koen Iterbeke<sup>b</sup>, Fred Stappers<sup>b</sup>, Paul Stevens<sup>b</sup>, Laurent Schueller<sup>a</sup>, Pieter Van Remoortere<sup>a</sup>, Guenter Kraus<sup>a</sup>, Piet Wigerinck<sup>a</sup>, Jan Rosier<sup>a</sup>

<sup>a</sup>Tibotec Inc., Gen. De Wittelaan 1718 3, 2800 Mechelen, Belgium

<sup>b</sup>Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium

### ARTICLE INFO

Article history:  
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### ABSTRACT

Long-acting parenteral formulations of antiretrovirals could facilitate maintenance and prophylactic treatment in HIV. Using the poorly water- and oil-soluble non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC278 (rilpivirine) as base or hydrochloride (HCl), nanosuspensions were prepared by wet milling (Elan NanoCrystal<sup>®</sup> technology) in an aqueous carrier. Laser diffraction showed that the average particles size were (1) close to the targeted size proportionality (200–400–800 nm), with increasing dis-

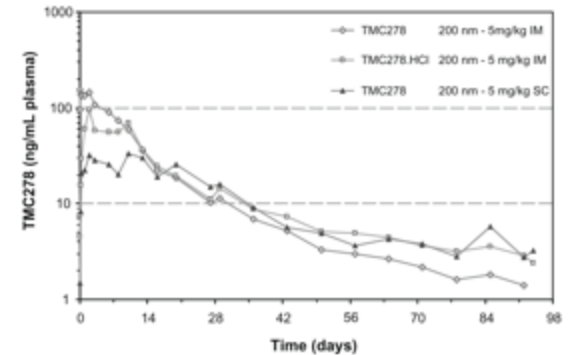


Fig. 2. Mean plasma concentration profiles (ng/mL) of TMC278 long-acting nanosuspensions in beagle dogs after SC and IM administration of 200 nm nanosuspensions at 5 mg/kg (base or HCl salt in mg equivalent).

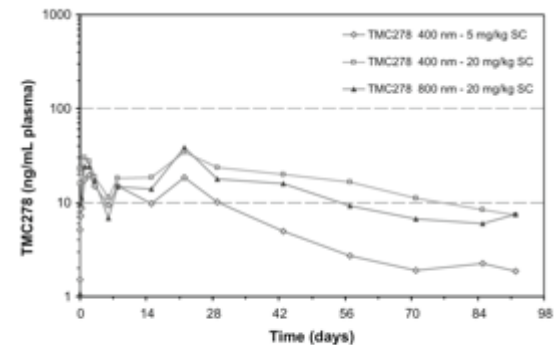
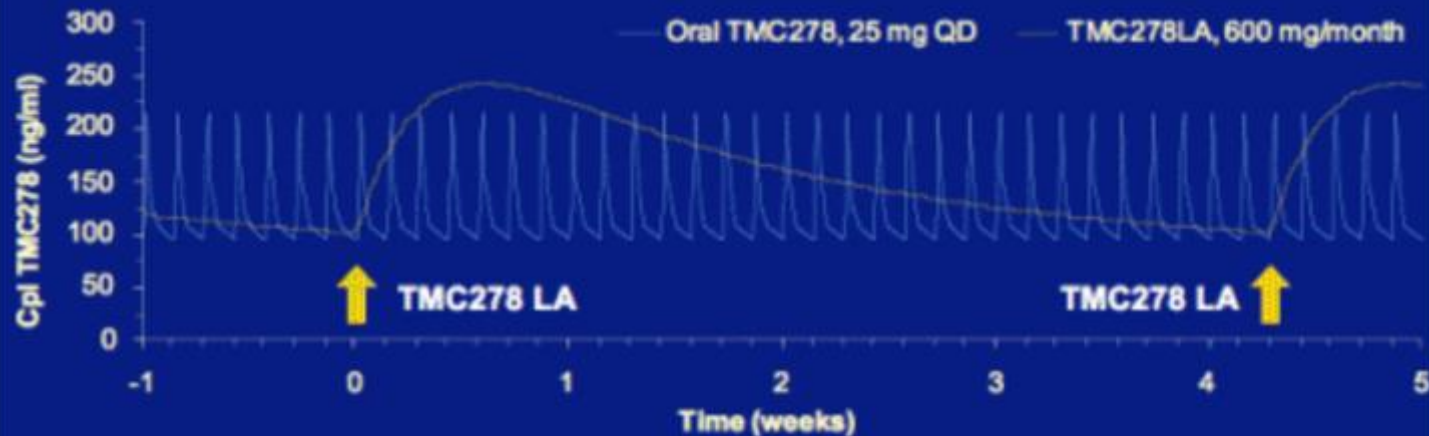


Fig. 3. Mean plasma concentration profiles (ng/mL) of TMC278 long-acting nanosuspensions in beagle dogs after SC dosing of 400 and 800 nm nanosuspensions at 5 or 20 mg/kg (TMC278 base).

# İlk Çalışmalar

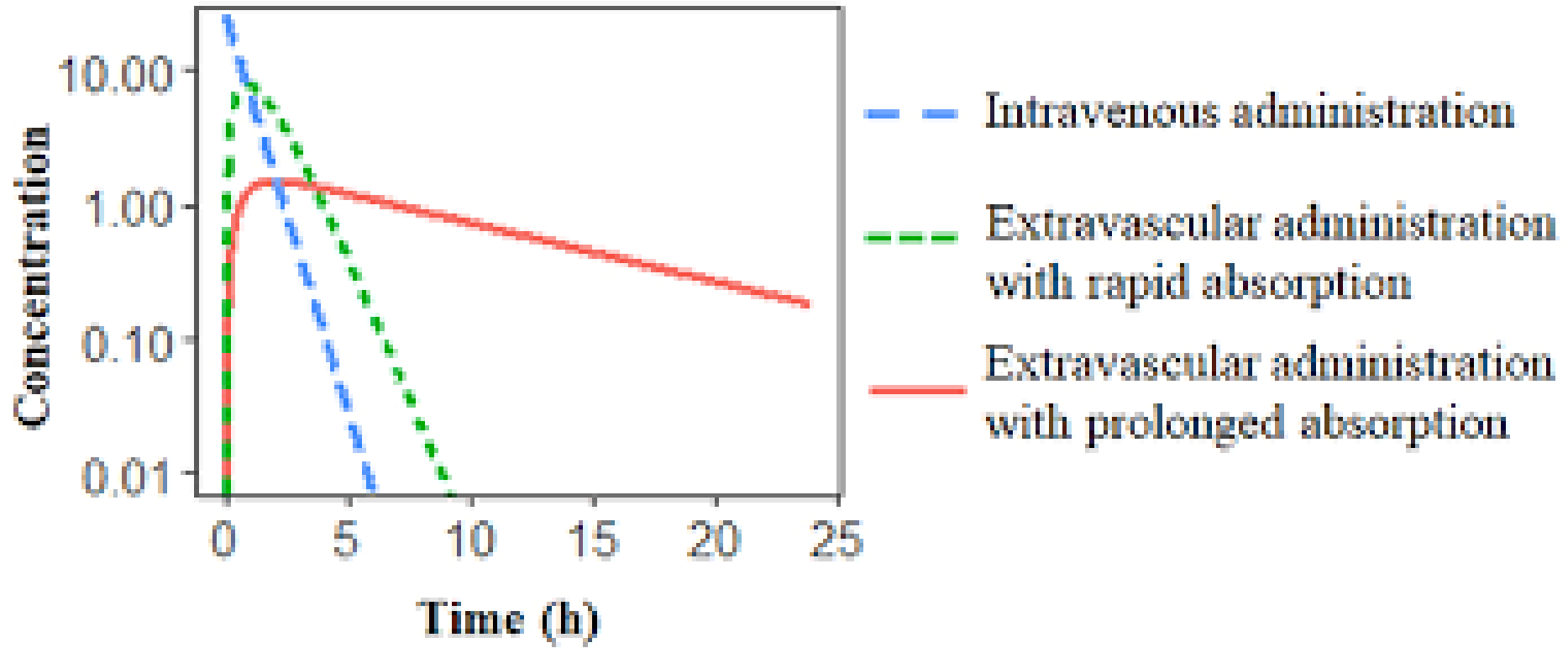
## Therapeutic concentrations achievable with monthly intramuscular injections

Steady-state simulations: TMC278 LA, 600mg/month, and oral TMC278 25mg qd



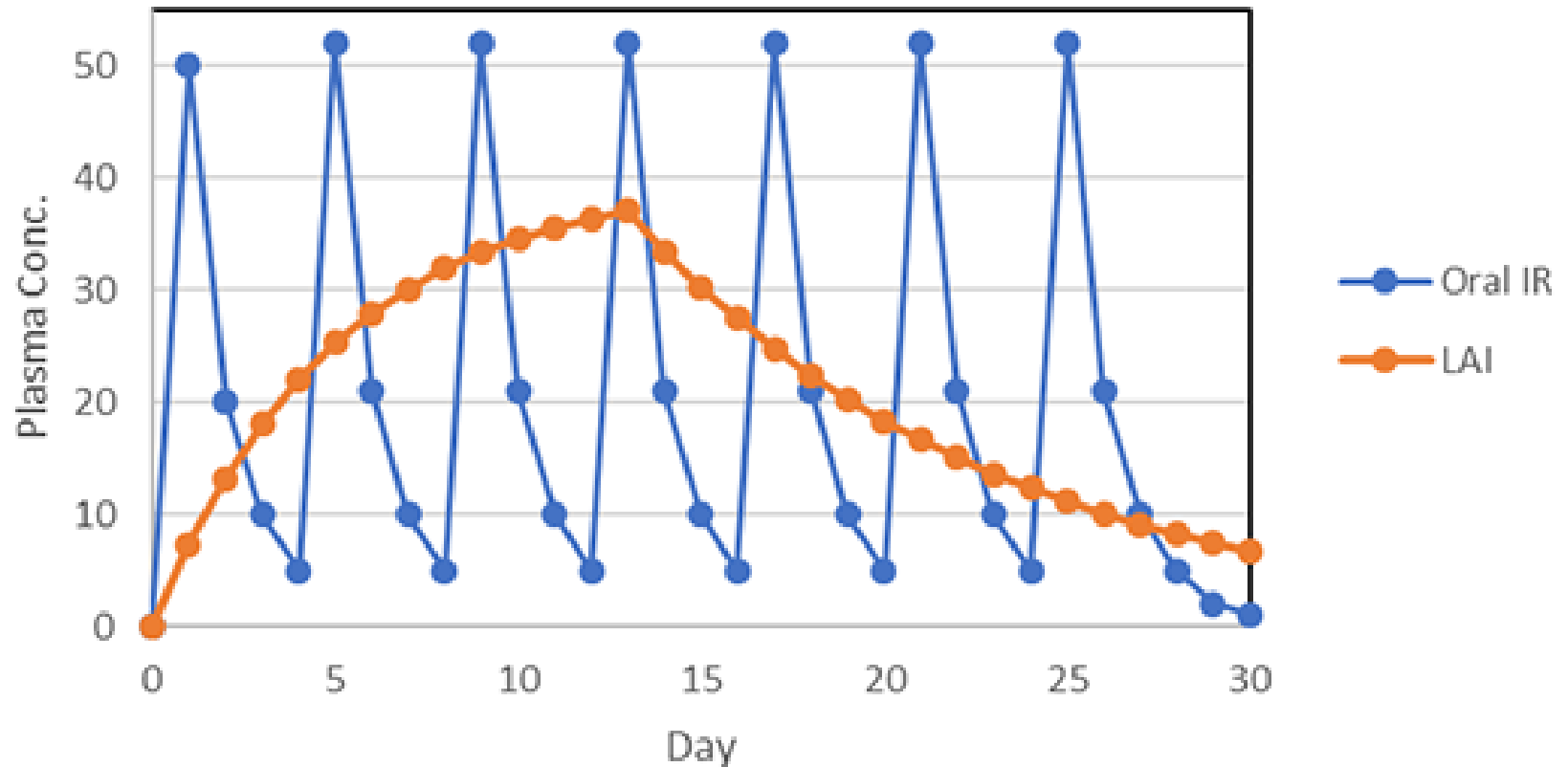
- Once monthly 600mg of TMC278 LA is predicted to achieve similar troughs as oral TMC278 25mg qd

# İlaç Uygulama Yolu ve Kan Düzeyi



# İlaç Uygulama Yolu ve Kan Düzeyi

Long Acting Injectable PK Profile vs Oral IR



# Uzun Etkiyi Sağlayan Teknoloji

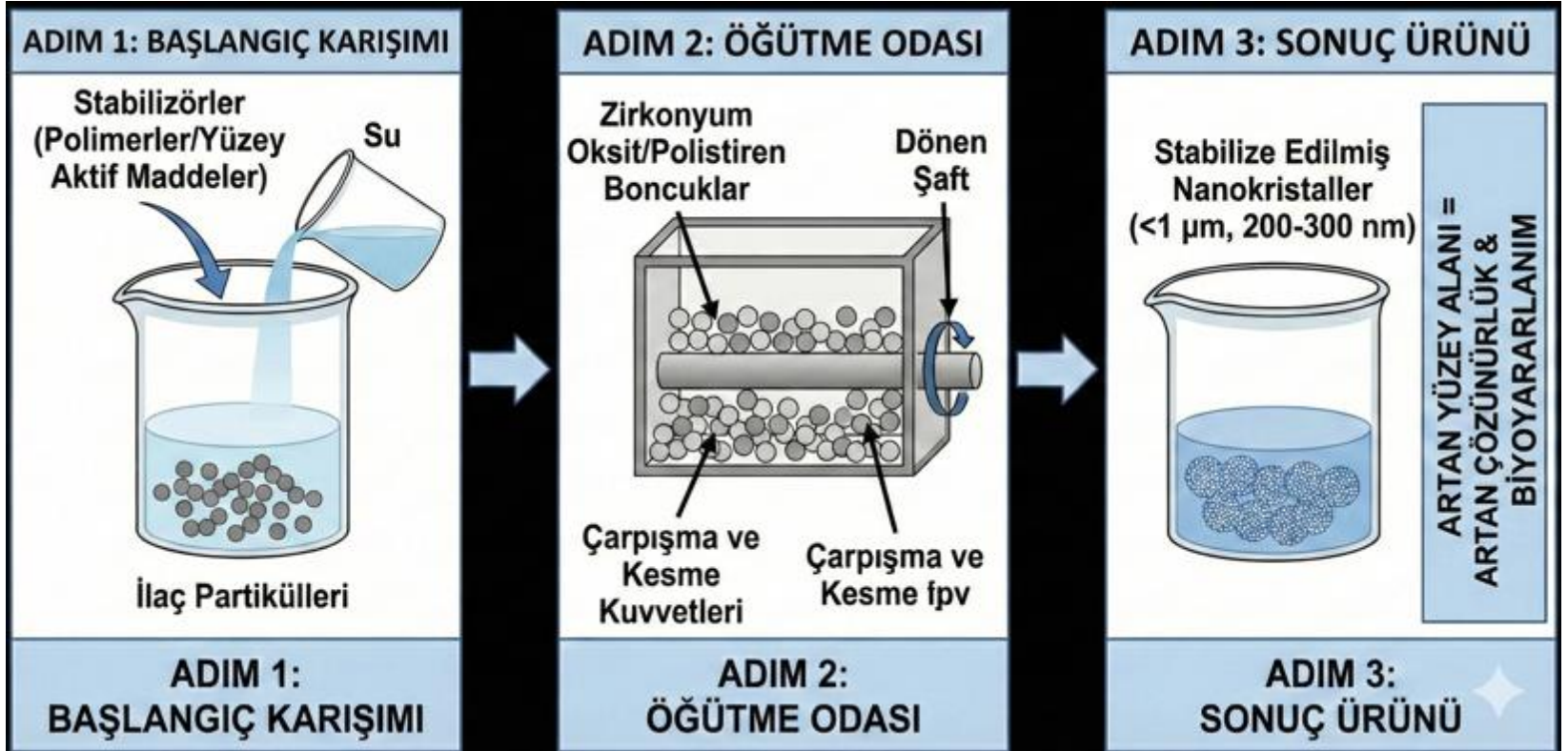
## ■ 1) Nanokristal / nanosüspansiyon IM depo

- Etkin madde **suda zor çözünen kristaller** halinde **~200 nm** boyuta indirgenir (nanomilling/yüksek basınçlı homojenizasyon gibi “top-down” süreçler).
- Aqueous **steril süspansiyon** + surfaktan/ıslatıcı ile stabil tutulur.

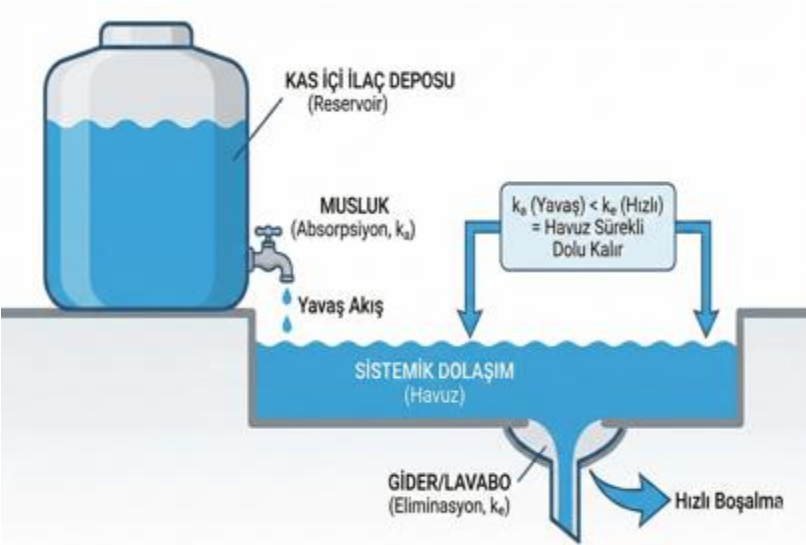
## ■ 2) Yüksek konsantrasyonlu SC “çözelti”

- Örnek: **Lenacapavir** SC enjeksiyon **çözelti** formunda; PEG bazlı solvent sistemi ve pH ile formüle edilir.

# Uzun Etkiyi Sağlayan Teknoloji II



# Uzun Etkiyi Sağlayan Teknoloji III



## Farmakokinetik (PK): "Flip-Flop" Kinetiği

Oral ilaç: hızlı emilim ve yavaş atılım.

LAI (Long Acting Injectable) sistemlerde ise

durum tam tersi; **"Flip-Flop Kinetiği"**

**Depo Etkisi:** İlaç kas içine (intramüsküler)

enjekte edildiğinde, katı bir "ilaç deposu"

oluşur.

**Absorpsiyon Sınırlı Eliminasyon:** İlacın

vücuttan atılma hızı, enjeksiyon bölgesinden

emilim hızından çok daha yüksektir.

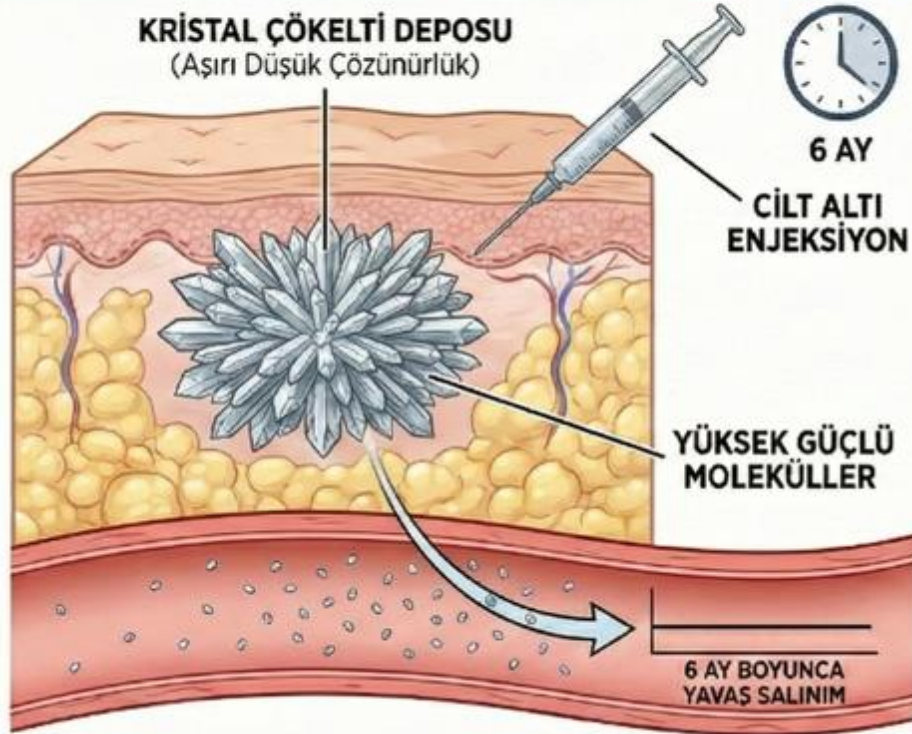
**Yavaş Salınım:** Nanokristaller düşük

çözünürlük nedeniyle yavaş yavaş çözünerek

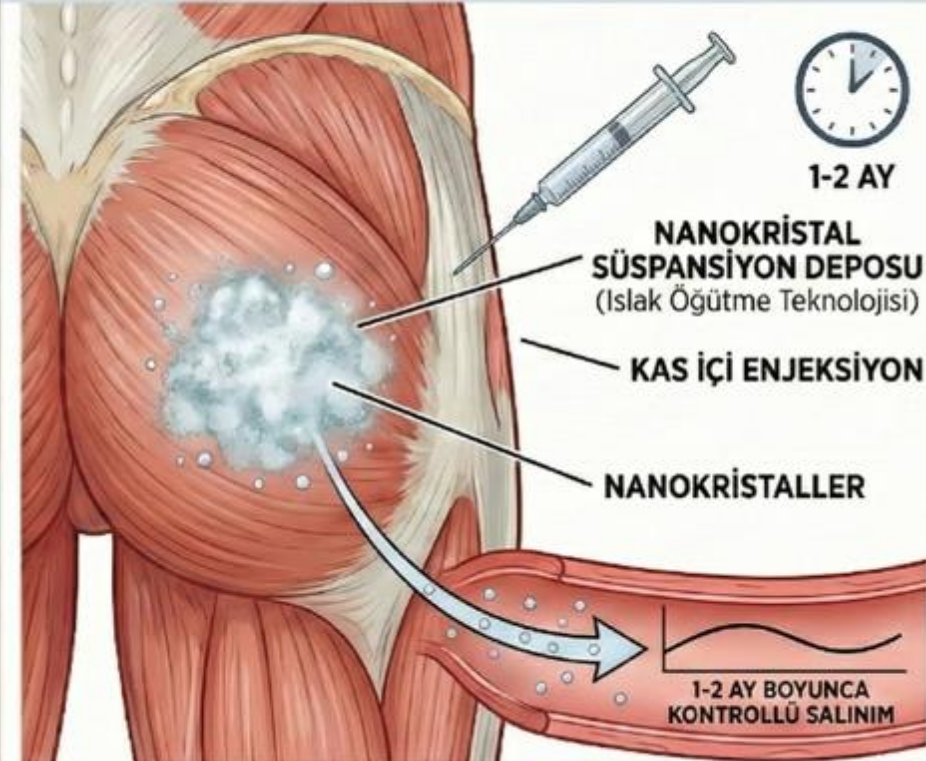
kana karışır.

# UZUN ETKİLİ HIV İLAÇLARI MEKANİZMASI: LENAKAVİR VE KABOTEGRAVİR

## LENAKAPAVİR (6 AYDA BİR)



## KABOTEGRAVİR (1-2 AYDA BİR)



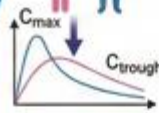
UZUN SÜRELİ ETKİNLİK

# Yavaş Salınım Çözüm mü?

## 1 Cinsiyet

Kadınlarda kas içi enjeksiyon (IM) emilimi ( $k_a$ ) daha yavaş. (Cabotegravir için %50.9 ↓).

Sonuç:  $C_{max}$  ↓,  $C_{trough}$  ↑.



## 2 Vücut Kitle İndeksi (BMI)

Yüksek BMI, emilimi ( $k_a$ ) yavaşlatır.

Kalın yağ dokusu iğneyi engeller, subkutan (SC) enjeksiyon riski.

Yağ dokusunun kanlanması az.



## 3 Enjeksiyon Bölgesi

Uyluk daha hızlı emilir ( $k_a$  ↑).

Kalça daha yavaş emilir ( $k_a$  ↓).

Uylukta terminal yarı ömür %26-39 daha kısa.



Emilim Hızı ( $k_a$ ) < Eliminasyon Hızı ( $k_e$ )



VS



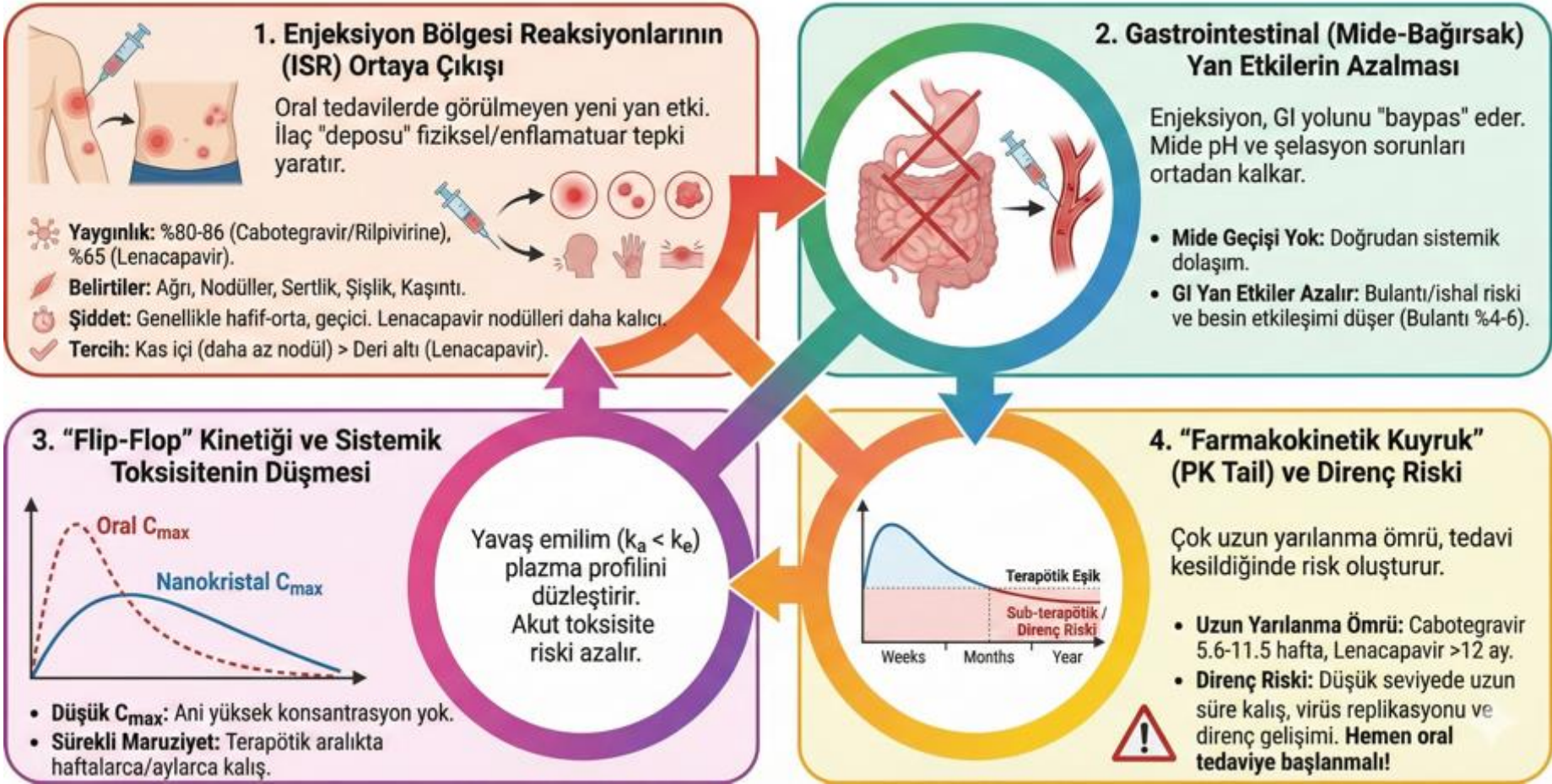
## 4 İlaç Partikül Boyutu

Nano-kristal (nanomilling) yüzey alanını artırır.

Uzun etkili formülasyonlar için suda çözünürlüğü düşük kristal formlar seçilerek çözünme hız kısıtlayıcı basamak olur.

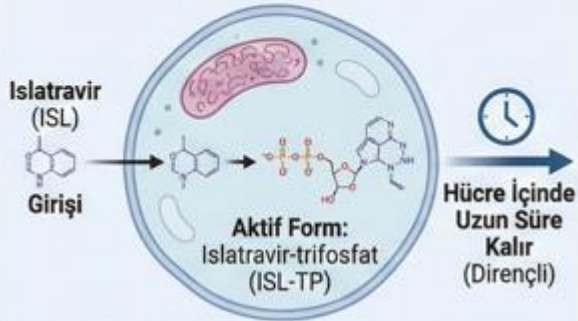
Dozlama Stratejisi (Etkilenir)

# Uzun Etkili Ama...



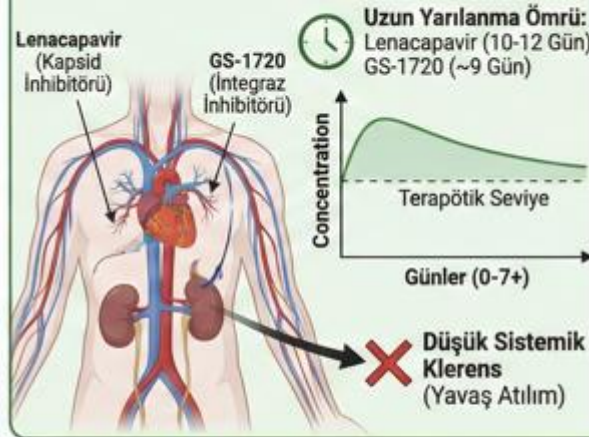
# Oral Uzun Etkili Formülasyon

## 1. Hücre İçi Birikim ve Yavaş Metabolizma (Islatravir Örneği)

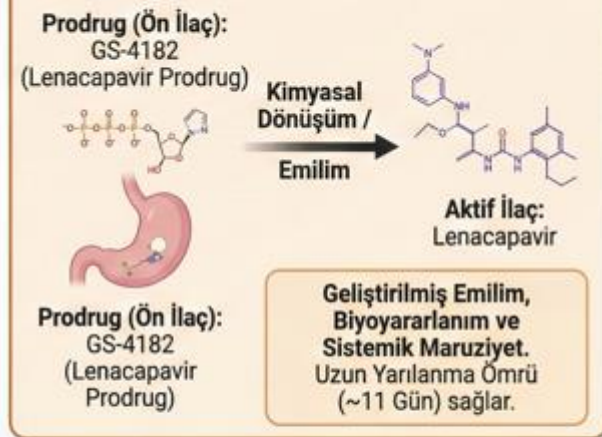


**Yüksek Potens:** Çok düşük dozda bile etkili (Örn: Haftalık 2 mg). Toksikite riski düşük.

## 2. Uzun Plazma Yarılanma Ömrü ve Düşük Klerens (Lenacapavir ve GS-1720)



## 3. 'Prodrug' (Ön İlaç) Kimyası ile Emilimin İyileştirilmesi



## Özet: Haftalık Oral Tedavinin Teknolojisi (Moleküler Mühendislik)



1. Vücuttan Çok Yavaş Atılım (Uzun Yarılanma Ömrü: 9-12 Gün)



2. Hücre içinde Aktif Formda Saklanma (Islatravir Mekanizması)



3. Yüksek Potens (Düşük Miktarda Yüksek Etkinlik)

Sonuç: Hastalar her gün yerine haftada bir kez ilaç olarak viral baskılamayı sürdürebilir.

# FDA/EMA Onaylı Uzun Etkililer, CAB/RPV

NDC 49702-253-15  
Rx Only

**CABENUVA**

Cabotegravir extended-release injectable suspension 400 mg/2 mL (200 mg/mL) co-packaged with Rilpivirine extended-release injectable suspension 600 mg/2 mL (300 mg/mL)

For gluteal intramuscular use only.  
Healthcare Professional administration only.

Store in refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused portion.

Prior to administration, bring vials to room temperature (not to exceed 25°C (77°F)). Vials may remain at room temperature for up to 6 hours. If not used within 6 hours, they must be discarded. **Ensure vial adapter is used correctly.**

400 mg/600 mg Kit

LIFT TO OPEN

Contents:

- 1 Cabotegravir single-dose vial
- 1 Rilpivirine single-dose vial
- 2 Vial adapters
- 2 Syringes
- 2 Injection needles (23 gauge, 1½ inch)
- 2 Syringe labels
- Prescribing Information
- Patient Information
- Instructions for Use

ViiV  
LABORATORIES

**BAŞLANGIÇ (ORAL DÖNEM)**

1 AY

KABOTEGRAVİR TABLET (30 mg)

RİLPİVİRİN TABLET (25 mg)

GÜNDE BİR KEZ, 1 AY BOYUNCA

**ENJEKSİYON BÖLGESİ (İNTRAMÜSKÜLER)**

HER İKİ İLAÇ İÇİN AYRI ENJEKSİYON

KALÇA KASI (DERİN KAS İÇİ ENJEKSİYONU)

**DOZLAMA (1 veya 2 AYDA BİR)**

1 AY

AYLIK DOZ (HER AY)

KAB (400mg/2mL) RİL (600mg/2mL)

İKİ AYLIK DOZ (HER 2 AYDA BİR)

2 AY

KAB (600mg/3mL) RİL (900mg/3mL)

HER ENJEKSİYON AYRI BİR KASA UYGULANMALIDIR.

**ÖNEMLİ NOT: SÜSPANSİYON HAZIRLIĞI**

KABOTEGRAVİR (Süspansiyon)

RİLPİVİRİN (Süspansiyon)

DOĞRU

YANLIŞ

BEYAZ RENKLİ, BULANIK SÜSPANSİYON. UYGULAMADAN ÖNCE İYİCE ÇALKALANMALIDIR.

# FDA/EMA Onaylı Uzun Etkililer, LEN

R<sub>x</sub> only

NDC 61969-3002-1

## Sunlenca<sup>®</sup> (lenacapavir) injection

**463.5 mg/1.5 mL (309 mg/mL)**

### For Subcutaneous Injection

#### Contents

- 2 x 1.5 mL lenacapavir single-dose vials
- 2 vial access devices
- 2 syringes
- 2 injection needles (22 gauge, 1/2 inch)
- Prescribing Information
- Instructions for Use
- Patient Information

Both 463.5 mg/1.5 mL (2 single-dose vials) must be administered to receive the 927 mg dose.

For Healthcare Professional administration only.



GILEAD

**BAŞLANGIÇ (YÜKLEME DOZU)**

Gün 1 Gün 2 Gün 8

**ORAL TABLETLELERLE BAŞLANGIÇ VEYA DOĞRUDAN ENJEKSİYON + TABLET**

**ENJEKSİYON BÖLGESİ (SUBKUTAN)**

5 cm Göbek Deliği

**KARIN BÖLGESİ (DERİ ALTI ENJEKSİYONU)**

**DOZLAMA (HER 6 AYDA BİR)**

2 x 1.5 mL 6 AY

**TOPLAM: 927 MG İLAÇ**

**ÖNEMLİ NOT: SOLÜSYON BERRAKLIĞI**

VIAL ACCESS DEVICE

SARI RENKLİ, BERRAK SOLÜSYON DOĞRU

YANLIŞ

# ATLAS2M, ART Deneyimli

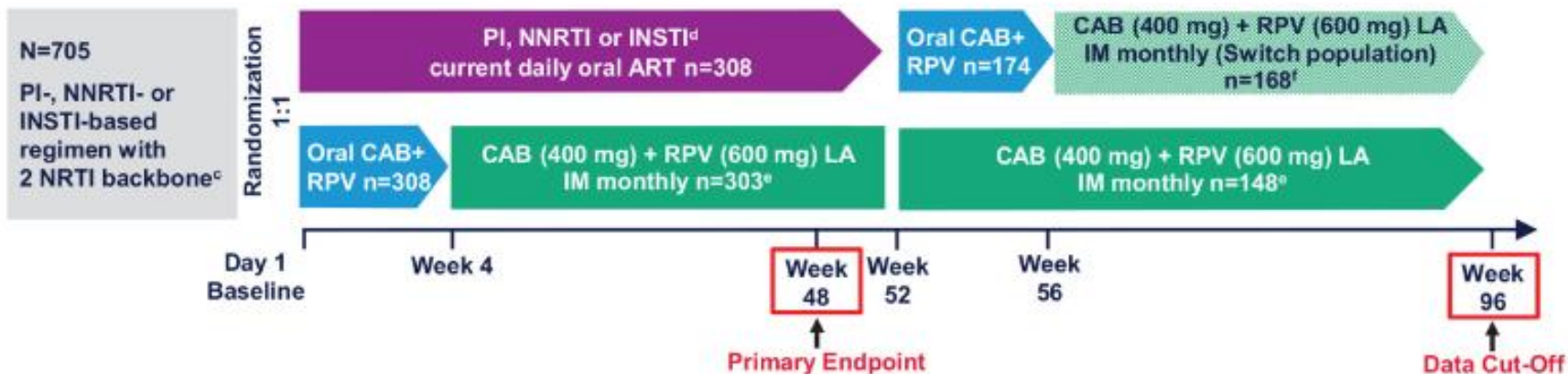
## Screening Phase

## Maintenance Phase

## Extension Phase<sup>a</sup>

243 participants transitioned to ATLAS-2M at the conclusion of the Maintenance Phase<sup>b</sup> (LA arm, n=132; CAR arm, n=111)

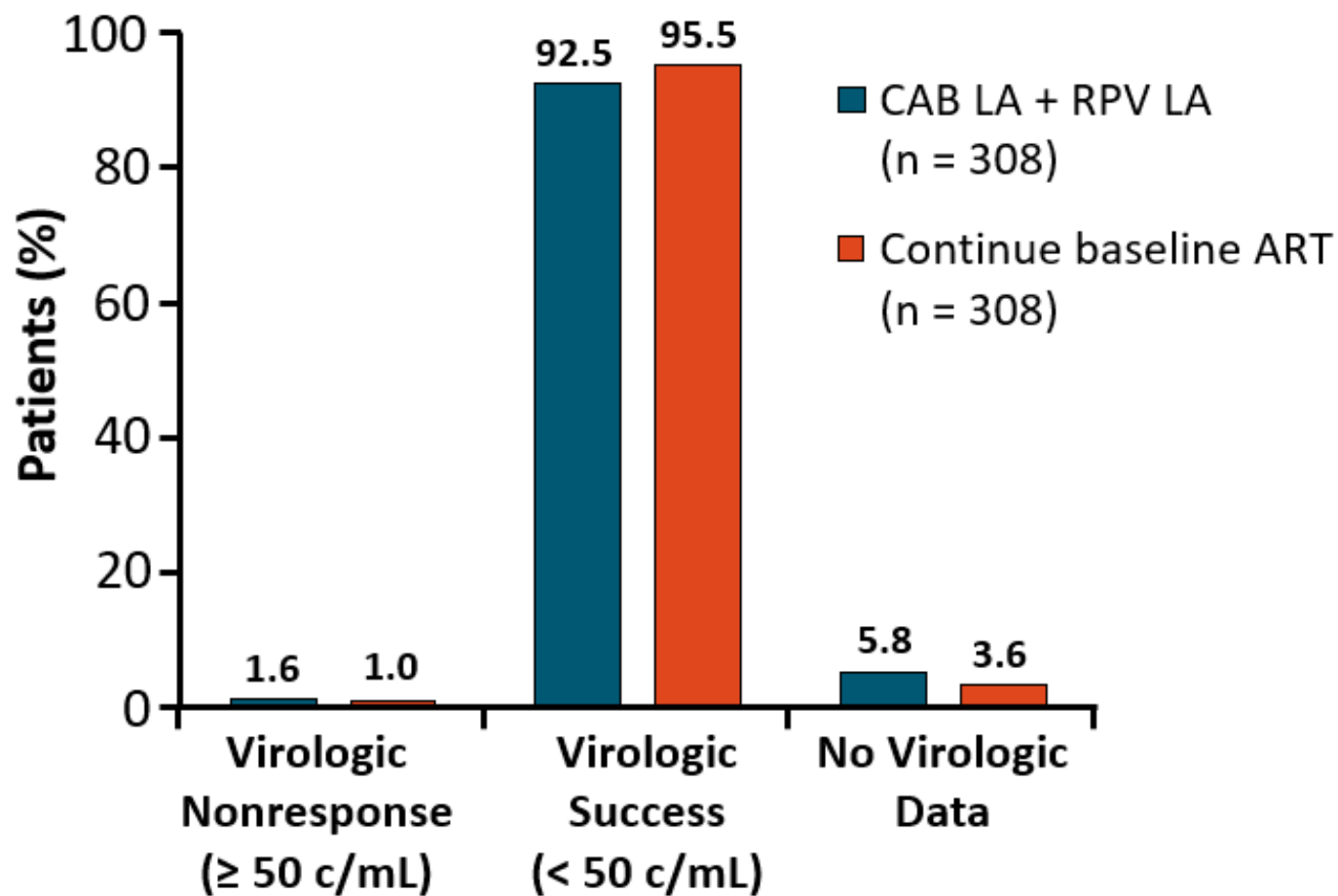
259 participants transitioned to ATLAS-2M throughout the duration of the Extension Phase (LA arm, n=121; Switch arm, n=138)



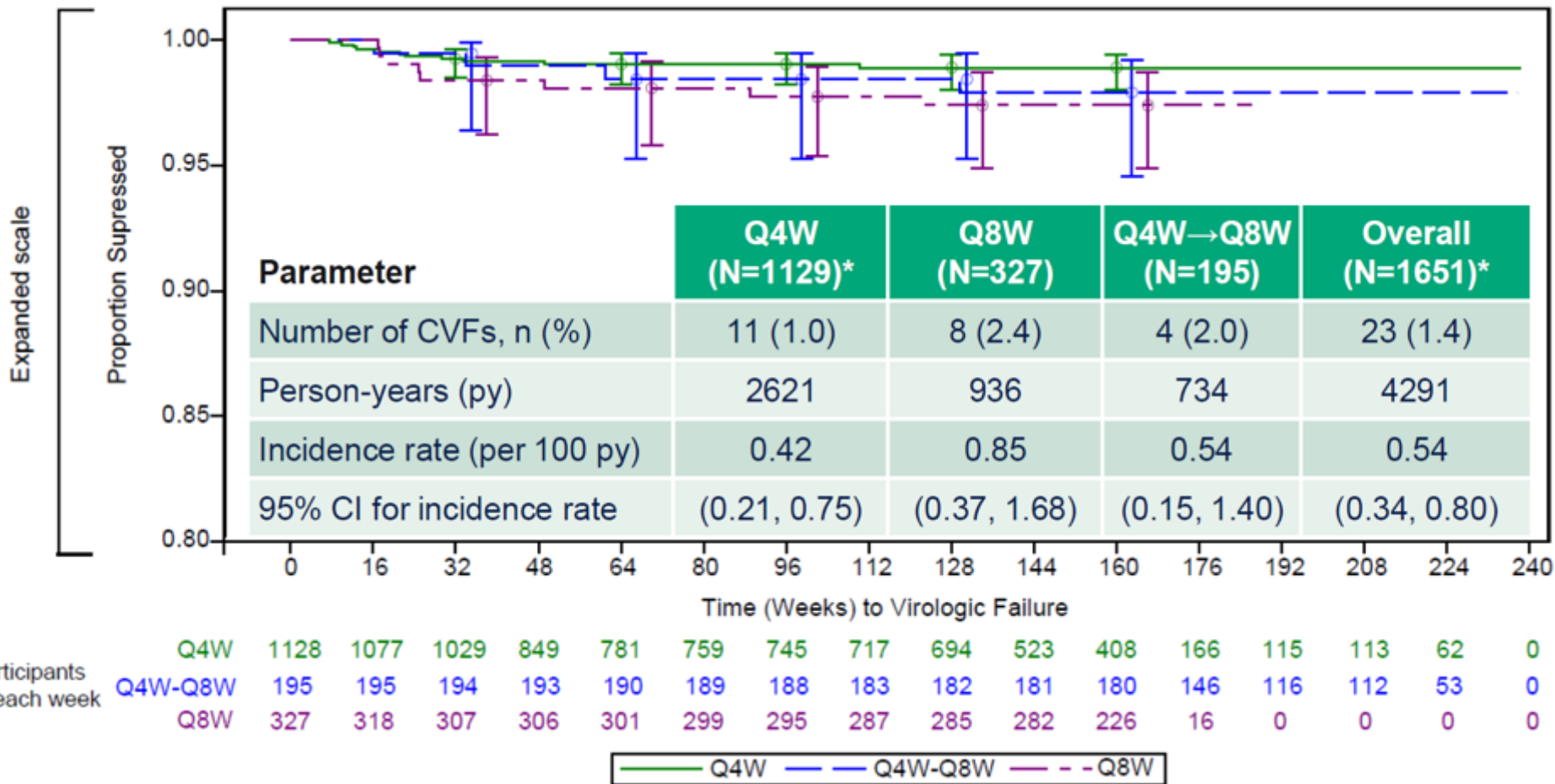
(a) Study design.

# ATLAS Primer Sonlanım

## Virologic Outcomes



# ATLAS2M Virolojik Başarısızlık



# ATLAS Virolojik Başarısızlık Anında RAM

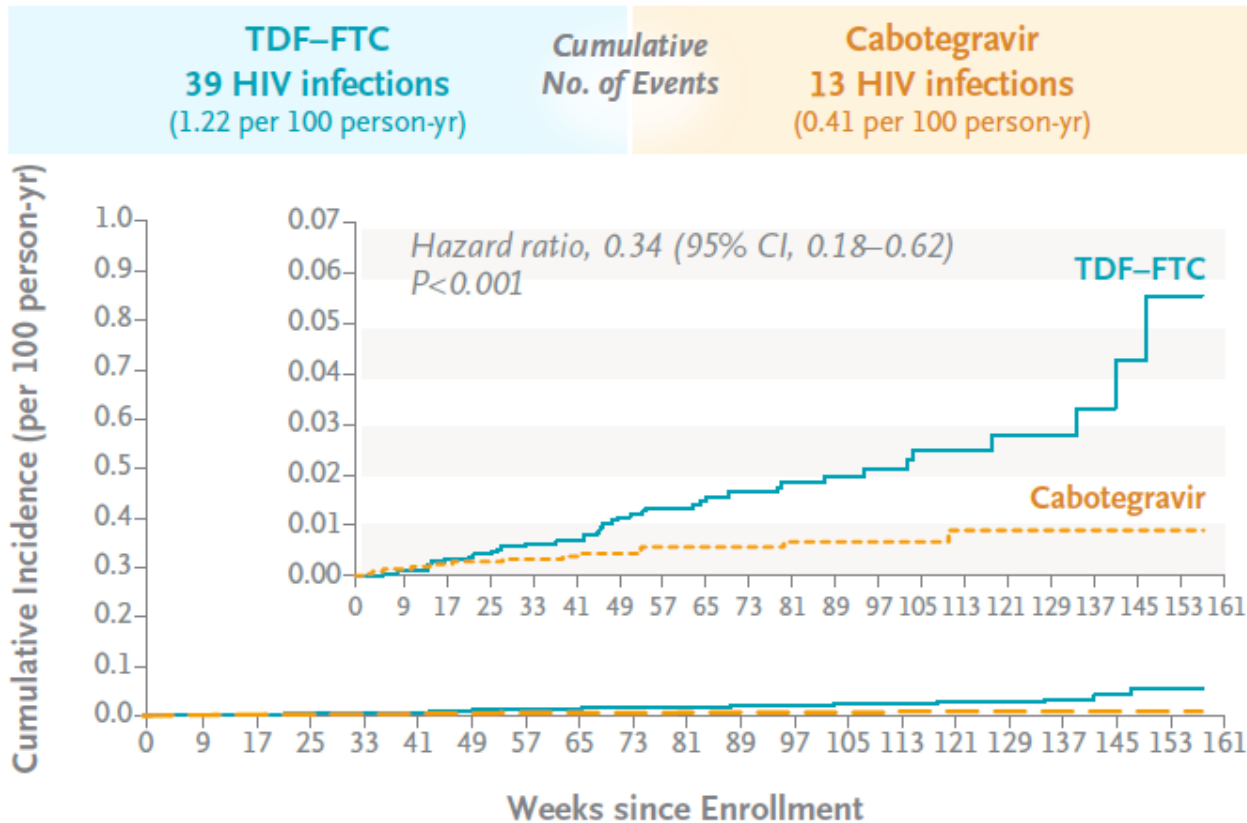
## CVF through Week 96 in ATLAS-2M

	n	CVFs; n (%)	CVFs with RPV RAMs	RPV RAMs at failure	CVFs with IN RAMs	IN RAMs at failure
Q8W	522	9 (1.7)	7/9	K101E E138E/K E 138A Y188L Y181C	5/9	Q148R N155H
Q4W	523	2 (0.4)	1/2	K101E M230L	2/2	Q148R N155H E138E/K

RAM = resistance associated mutation; RPV = rilpivirine; IN = integrase

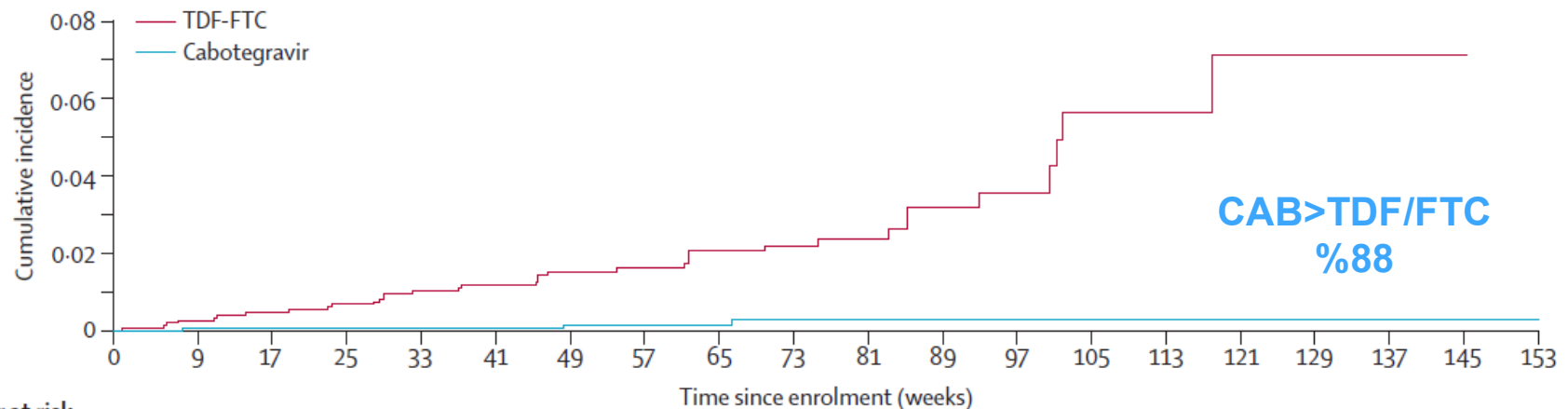
# Farklı İhtiyaçlar; Yeni Seçenekler

## Incident HIV Infection



Landovitz RJ et al. 2021 *Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women* N Engl J Med

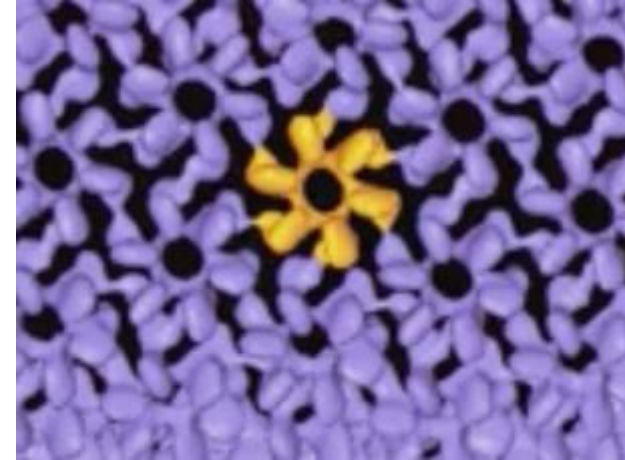
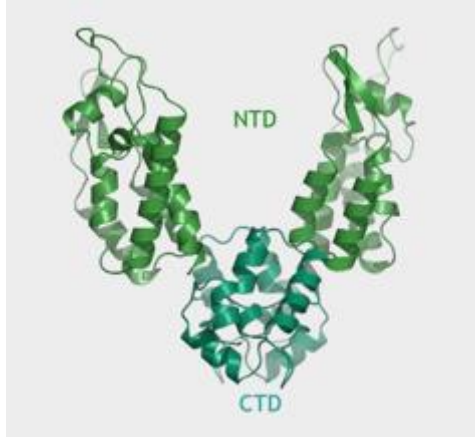
# Farklı İhtiyaçlar; Yeni Seçenekler



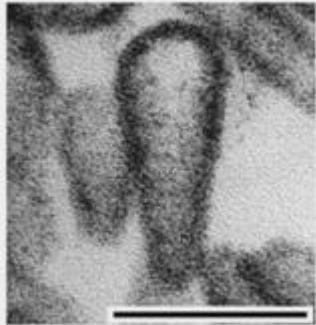
		0	9	17	25	33	41	49	57	65	73	81	89	97	105	113	121	129	137	145	153	
<b>Number at risk</b>																						
TDF-FTC	1610	1490	1429	1410	1353	1260	1160	984	800	656	485	306	201	115	70	63	52	22	3	0		
Cabotegravir	1614	1488	1441	1429	1371	1279	1181	988	801	647	482	304	204	116	67	58	50	23	3	2		
<b>Cumulative number of events</b>																						
TDF-FTC	0	4	7	10	15	17	21	22	26	27	28	31	32	35	35	36	36	36	36	36	36	
Cabotegravir	0	1	1	1	2	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	

Delany-Moretlwe S et al 2022 *Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial* Lancet

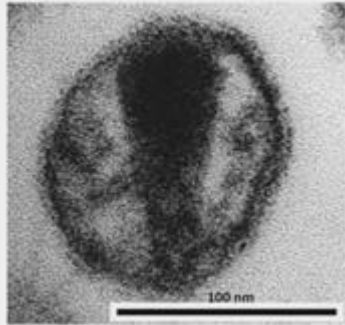
# Tavşan Kulakları



Pure HIV CA-NC Protein

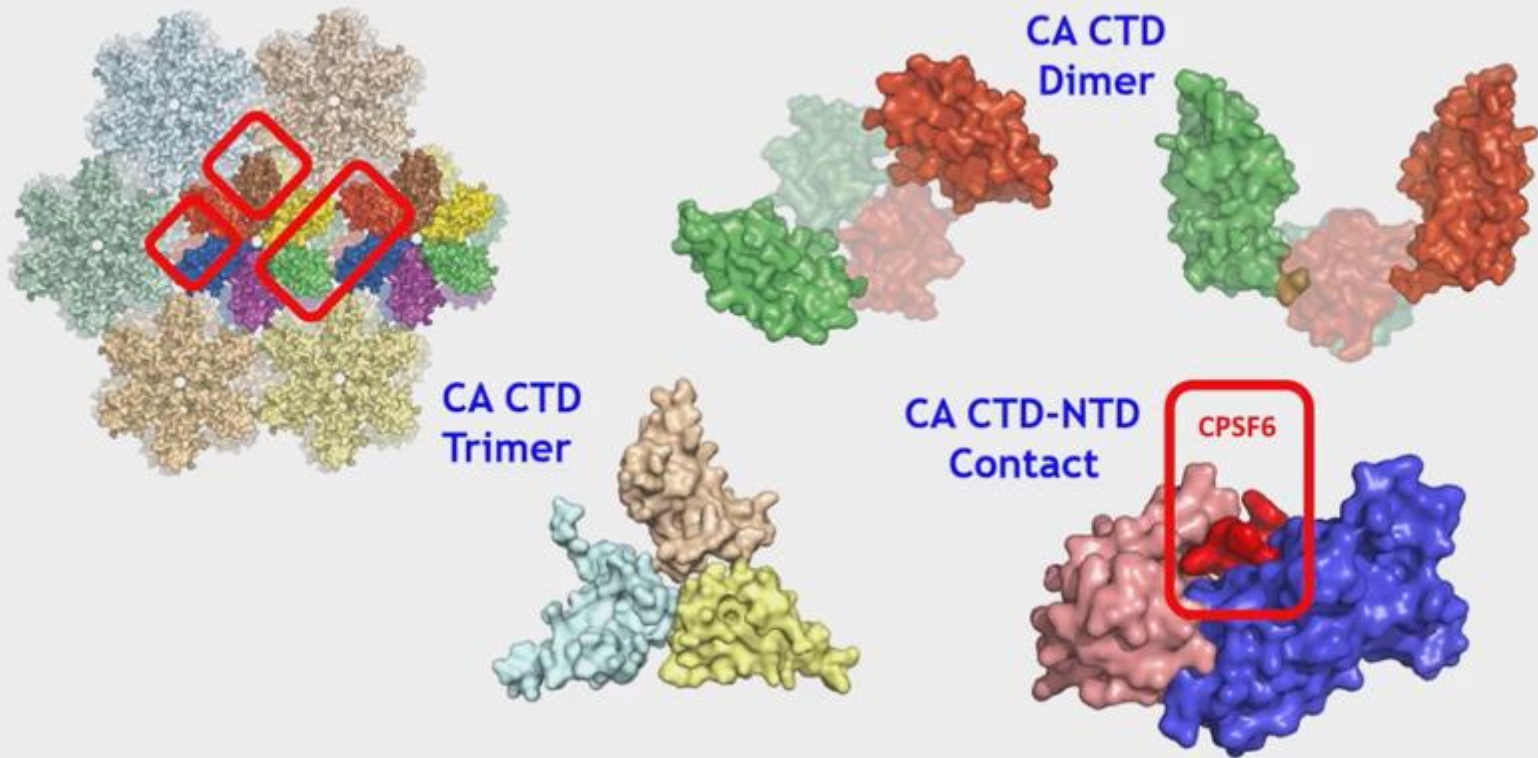


HIV-1

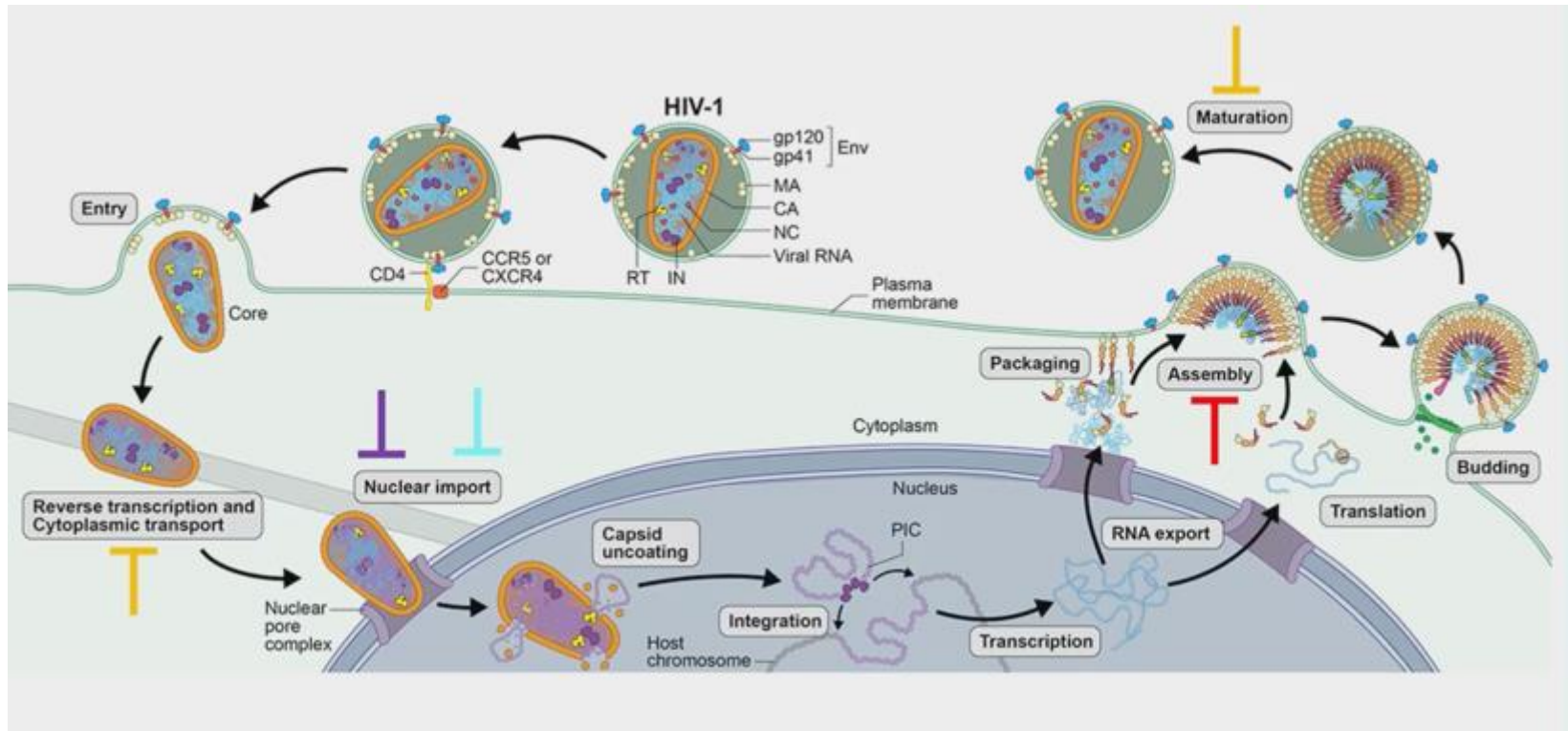


# Biraz Daha Kapsid Biyolojisi

## Interfaces in the Hexagonal HIV-1 CA Lattice

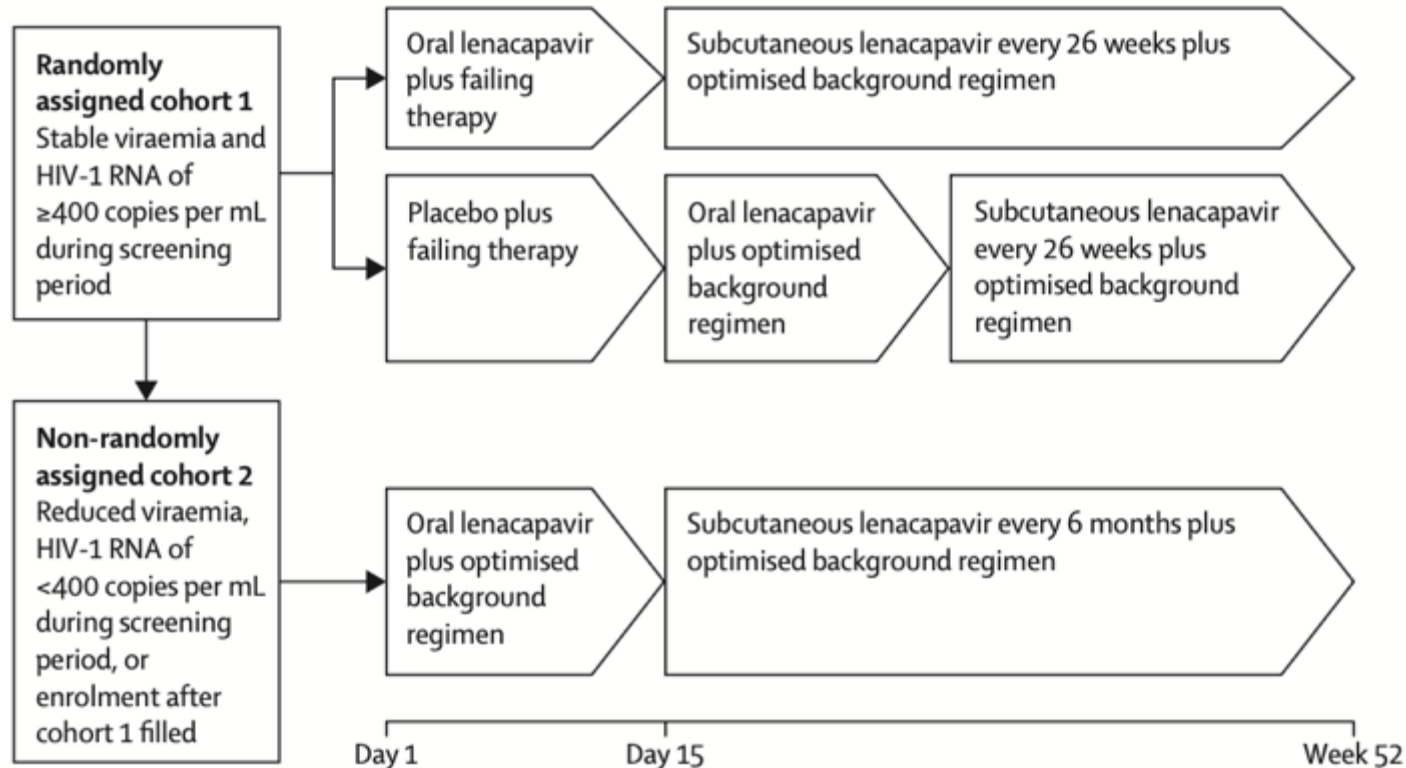


# LEN Nasıl Çalışır?



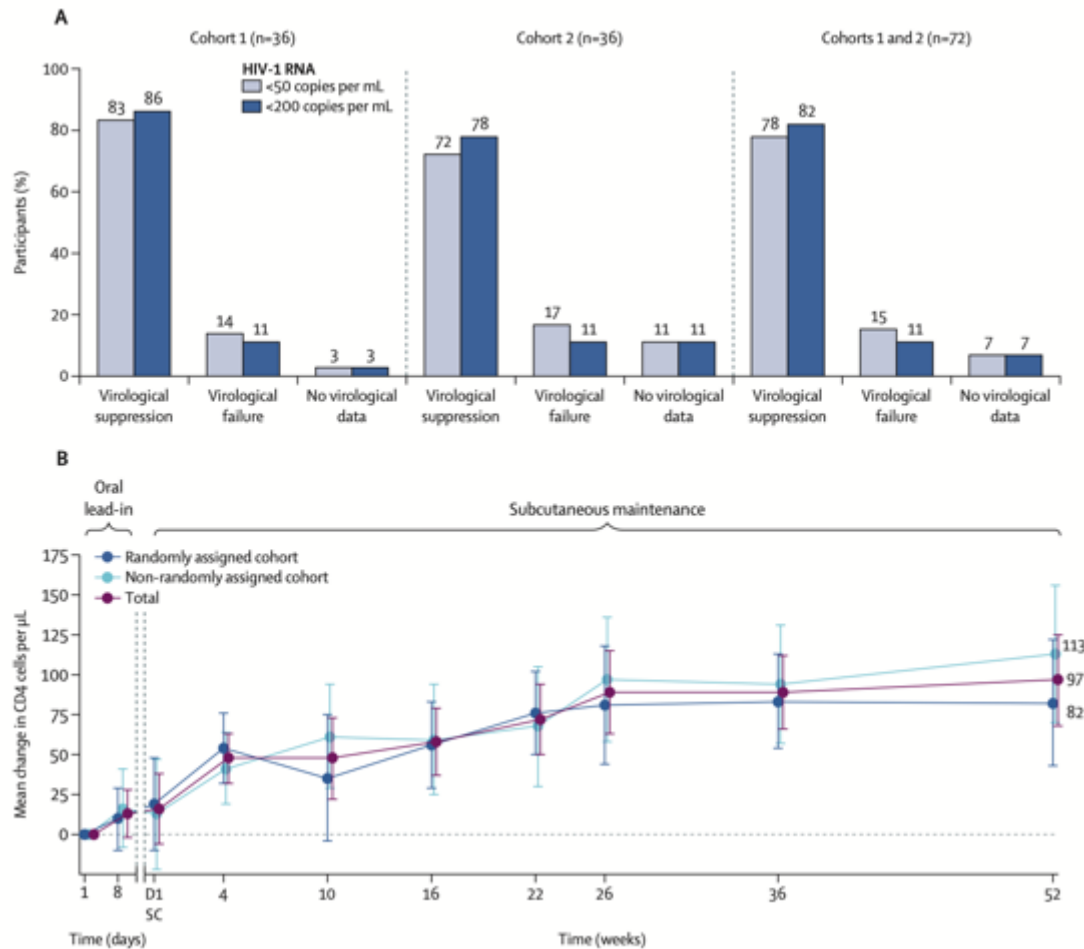
# Farklı İhtiyaçlar; Yeni Seçenekler

## A Trial design



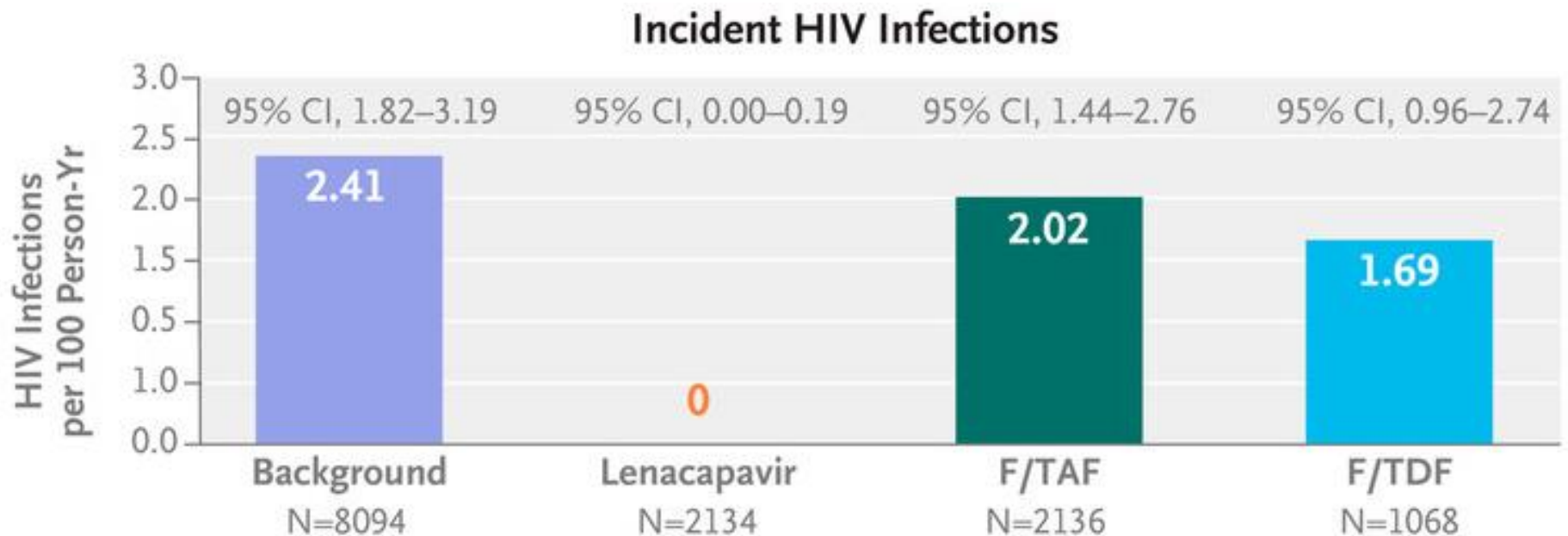
Ogbuagu O et al 2023 *Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial* Lancet HIV

# Farklı İhtiyaçlar; Yeni Seçenekler



Ogbuagu O et al 2023 *Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial* Lancet HIV

# Farklı İhtiyaçlar; Yeni Seçenekler



# Gelecek

## Yılda Bir Enjeksiyon: HIV Tedavisinde Geleceğin Teknolojileri

### Yaklaşım 1: İlacın Kimyasını Değiştirmek ("Ön İlaç" Teknolojisi)



Standard molecules



Fatty acid molecules



Nanostructures

**LASER ART: İlaçlar "Ön İlaç" Haline Getiriliyor**  
İlaçlara yağ asitleri eklenerek suda çözünmeleri engellenir ve nanokristal yapıya dönüştürülür.

### Bağışıklık Hücreleri Canlı "İlaç Deposu" Oluyor

Makrofajlar bu ilaç kristallerini yutar ve virüsün saklandığı dokulara "Truva Atı" gibi taşır.



### Sonuç: 1 Yıla Varan Etkin Koruma

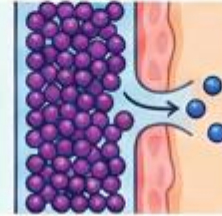
İlaç, makrofaj hücrelerinin içinde yavaşça aktifleşerek uzun süreli salınım sağlar.



### Yaklaşım 2: İlacın Sunumunu Değiştirmek (Yeni Formülasyon ve Cihazlar)

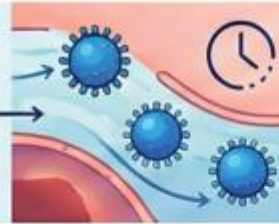


Etanol



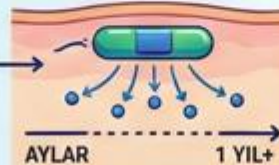
### Yüksek Yoğunluklu Enjeksiyonlar

Yıllık doz için ilacın yoğunluğu artırılır ve enjekte edilebilirliği sağlamak için formüle etanol eklenir.



### Ultra Uzun Etkili Süspansiyonlar (ULA)

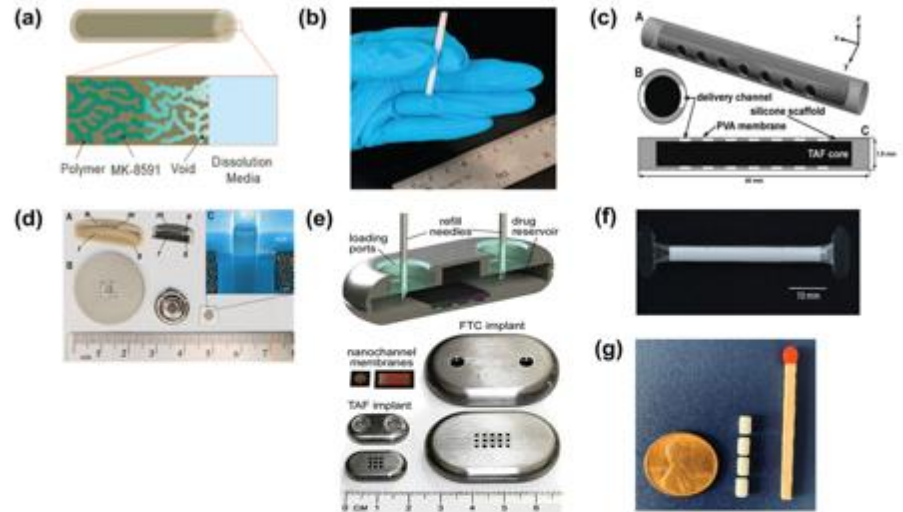
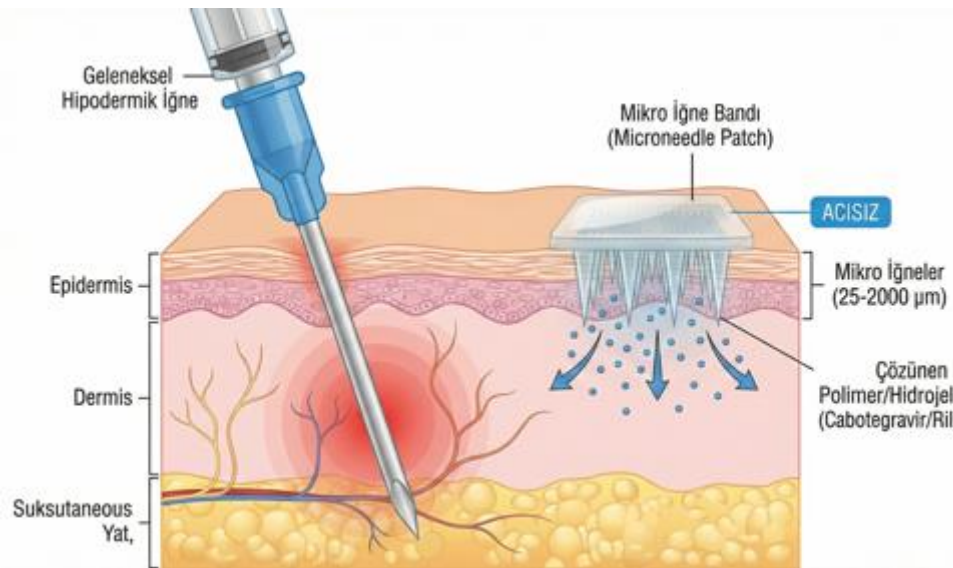
İlaç partiküllerinin özellikleri değiştirilerek ilacın vücuttaki yan ömrü 6 katına kadar uzatılabilir.



### Biyobozunur İmplantlar

Deri altına yerleştirilen küçük cihazlar, ilacı bir yıl veya daha uzun süre boyunca sürekli salabilir.

# Gelecek II



**Figure 2.** Long-acting (LA) subdermal/subcutaneous implants in clinical development. **(a)** Merck EFdA implant (Reproduced with permission from [35]); **(b)** RTI thin film TAF implant (Reproduced with permission from [85] under the terms and conditions of the Creative Commons Attribution (CC BY) license <http://creativecommons.org/licenses/by/4.0/>); **(c)** Oak Crest TAF subdermal implant (Reproduced with permission from [95]) (Three-dimensional model (A) and cross-sectional drawings (B and C) of TAF implant. The TAF core (black) inside the silicone scaffold with PVA membrane coating is shown (not to scale). Cross sections were sliced through the y-z (B) and x-y planes (C). **(d)** HMRI nanofluidic refillable CAB implant (Reproduced with permission from [98]) ((A) Rendered image of cross-section of polyether ether ketone (PEEK) (left) and titanium (right) drug reservoirs. (B) Assembled PEEK βCAB (left) and titanium CAB (middle) drug reservoirs and 13 nm nanofluidic membrane (right). (C) SEM image of nanochannel membrane cross-section

## Long-acting approaches for the treatment and prevention of HIV

Agent	Route of Administration	Potential Indication	Stage of Development	References
Islatravir	Oral	HIV PrEP	Phase 1b	18–23
Gastric residence device	Oral	HIV treatment and PrEP	Preclinical	29
Maraviroc, efavirenz, and lopinavir solid drug nanoparticle formulations	Oral	HIV PrEP	Preclinical	30–32
Darunavir/ ritonavir nanoparticle-in-microparticle delivery system (NiMDS)	Oral	HIV PrEP	Preclinical	33
EFV, lopinavir, and darunavir nanoemulsifying systems	Oral	HIV PrEP	Preclinical	34–36
Tenofovir alafenamide fumarate patch	Transdermal	HIV PrEP	Preclinical	40
Rilpivirine microneedle patch	Transdermal	HIV PrEP	Preclinical	41
Dapivirine ring	Vaginal	HIV PrEP	Phase 3	50, 51
Tenofovir and levonorgestrel ring	Vaginal	HIV PrEP	Phase 1	52
3BNC117	Intravenous infusion	HIV PrEP	Phase 1	67
VRC01LS	Intravenous infusion or subcutaneous injection	HIV PrEP	Phase 1	68
3BNC117 + 10-1074	Intravenous infusion	HIV treatment and PrEP	Phase 1b	71, 72
Nevirapine implant	Subcutaneous	HIV PrEP	Preclinical	79
Dolutegravir implant	Injectable (subcutaneous)	HIV PrEP	Preclinical	82
Islatravir implant	Subcutaneous	HIV PrEP	Phase 1	84, 85
Tenofovir alafenamide fumarate implant	Subcutaneous	HIV PrEP	Preclinical	86–88
Refillable emtricitabine and tenofovir alafenamide fumarate implant	Subcutaneous	HIV PrEP	Preclinical	89
Cabotegravir nanofluidic implant	Subcutaneous	HIV PrEP	Preclinical	90
Long acting cabotegravir and rilpivirine (cabenuva)	Injectable (intramuscular)	HIV treatment and PrEP	Phase 3- USA Approved-Canada	96–99, 101,102
Long acting capsid inhibitor (GS-6207)	Injectable (subcutaneous)	HIV treatment	Phase 1	103, 104
Dolutegravir, lamivudine, emtricitabine, abacavir, rilpivirine, and cabotegravir LASER-ART	Injectable (intramuscular)	HIV PrEP	Preclinical	107–113, 120

# Özet

- Gelecek çok güzel seçeneklere gebe
- One size does not fit all
- Korunmada
- Küre giden yolda...