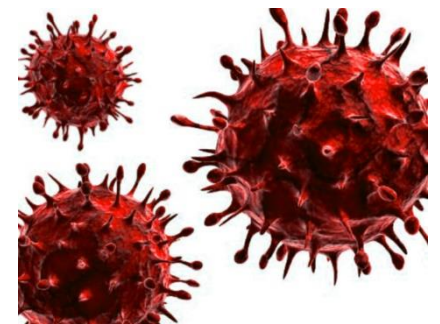


HIV RESISTANCE TO ART

Lessons from fundamental research

Gilles Darcis, CHU de Liège



HIV drug resistance

- At the end of December 2022, 29.8 million people were accessing ART, up from 7.7 million in 2010
- Increased use of HIV medicines has been accompanied by the emergence of HIV drug resistance, the levels of which have steadily increased in recent years.
- All antiretroviral drugs, including those from newer drug classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant virus.

HIV drug resistance

Key facts (9 May 2024)

- The emergence of acquired resistance to Dolutegravir (DTG) – the preferred antiretroviral drug – is higher than anticipated
- DTG resistance amplifies the urgent need to **implement standardized surveys** to characterize the prevalence and patterns of DTG resistance mutations and their associated clinical determinants.
- As the use of dolutegravir-based antiretroviral treatment (ART) is scaled up, remaining vigilant in **preventing and monitoring HIV drug resistance** among infants newly diagnosed with HIV is imperative.



World Health
Organization

HIV drug resistance

HIV drug resistance

Brief report 2024



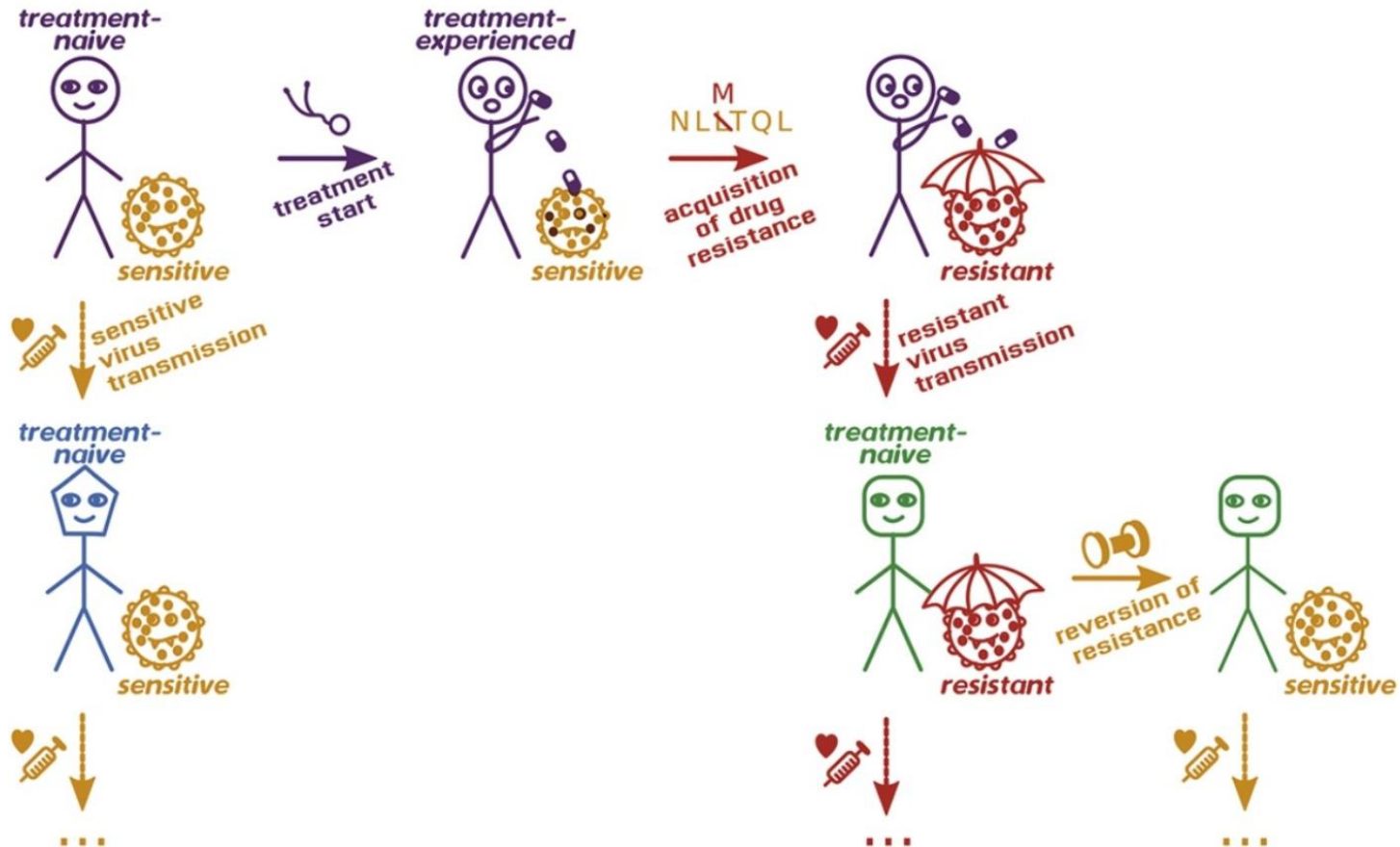
Table 4. HIV drug resistance to DTG among adults receiving DTG-based ART in PEPFAR-supported surveys, 2020–2022

Country	Method	Sample size genotyped	Inclusion criteria	Year of sample collection	Prevalence of DTG resistance
Uganda	Laboratory-based	457 (255 amplified)	<ul style="list-style-type: none"> At least nine months on a DTG-based regimen Dried blood spots or plasma test with viral load ≥ 1000 copies/mL ≥ 15 years of age 	2021–2022	3.9% ^a
Ukraine	Laboratory-based	366 (315 amplified)	<ul style="list-style-type: none"> At least nine months on a DTG-based regimen Plasma viral load ≥ 1000 copies/mL >18 years of age 	2020–2021	6.6% ^a
Mozambique	Clinic-based	193 (183 amplified)	<ul style="list-style-type: none"> Treatment-experienced people transitioned to TLD experienced persistent failure to suppress viral load (viral load >1000 copies/mL) >18 years of age 	2021–2022	19.6%
Malawi	Clinic-based	213 (212 amplified)	<ul style="list-style-type: none"> At least nine months on a DTG-based regimen Viral load ≥ 1000 copies/mL ≥ 15 years of age 	2020–2021	8.6% ^a



HIV drug resistance

- acquired resistance
- transmitted resistance

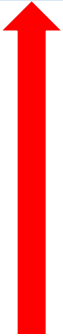


HIV drug resistance



Adherence, Virological Failure and Second Line ART

- Virological failure (defined on page 17) is almost always due to suboptimal ART adherence, and always requires adherence assessment and support
- Resistance testing is recommended where possible. Choice of second line therapy is dependent on ALL previous ART exposure and documented cumulative HIV resistance mutations at all times tested



HIV drug resistance



Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV

- All prior and current drug-resistance test results, when available, should be reviewed and considered when constructing a new regimen for a patient **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

HIV drug resistance

Consequences of Resistance to multiple antiretroviral drugs among people living with HIV (PLWH)


high pill burden

Toxicity

drug interactions

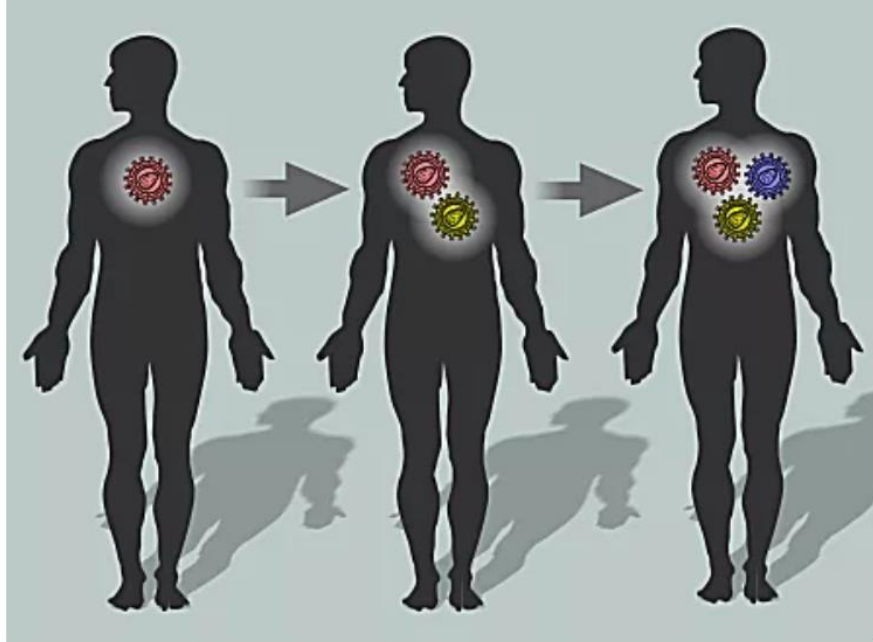
10 Things You Should Know About HIV Drug Resistance

By [James Myhre & Dennis Sifris, MD](#) | Updated on June 06, 2022

Print 

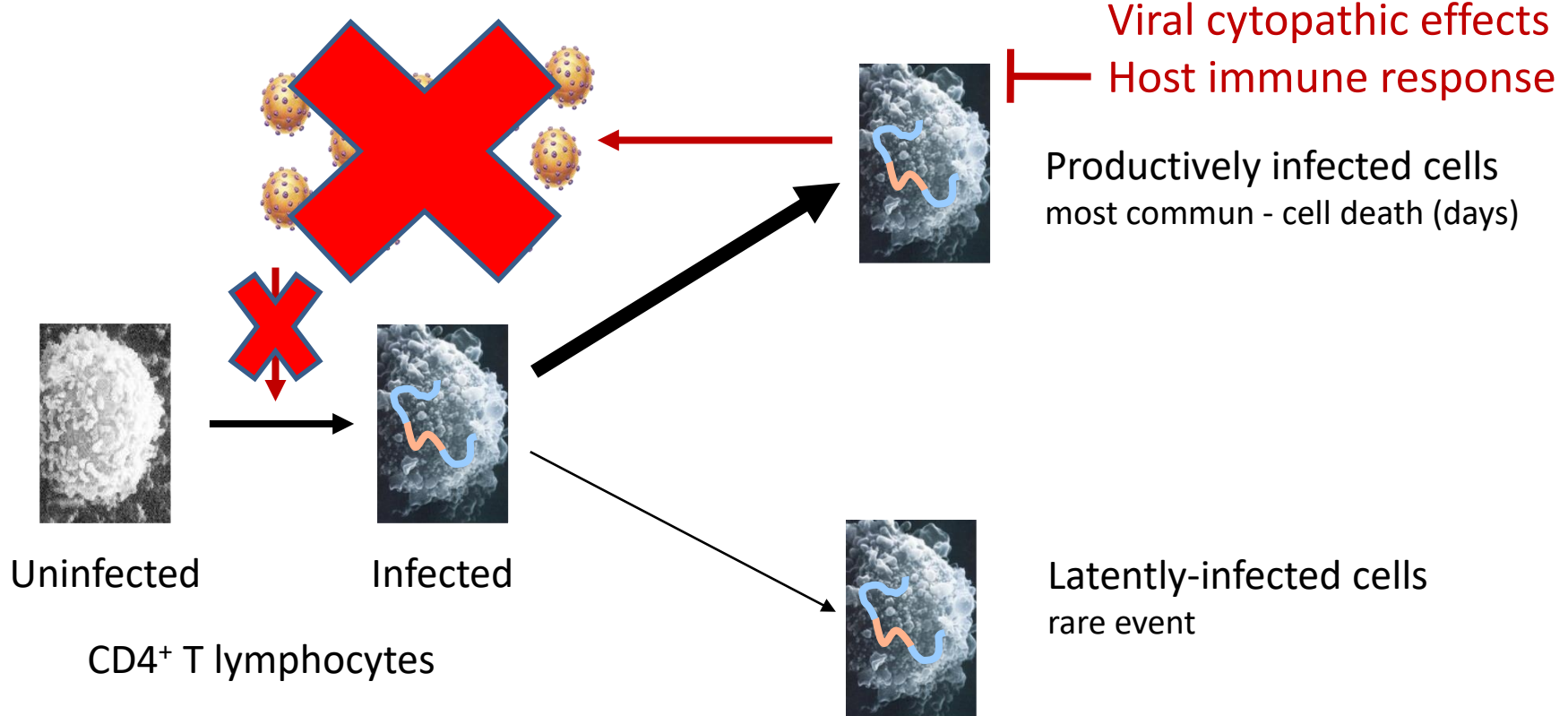
✓ Medically reviewed by [Isaac O. Opole, MD, PhD](#)

10 Resistance Is Not Futile, but It Is Forever

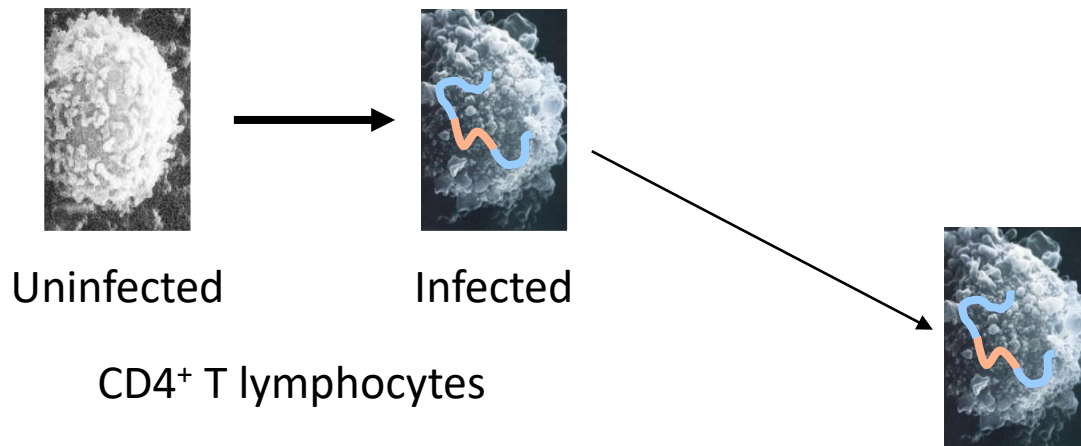


WHY DO RESISTANT VIRUSES PERSIST?

TREATMENT



WHY DO RESISTANT VIRUSES PERSIST?



HIV-1 RESERVOIRS

Latently-infected cells
rare event

SUMMARY

- **HIV Resistance is still an issue**
- **HIV resistance is cumulative because HIV (WT and resistant proviruses) persist in the reservoir**
- **This necessitates intensive therapeutic intervention using non-standard combinations of substances and, in some cases, with a variety of substances, leading to comprehensive ART**

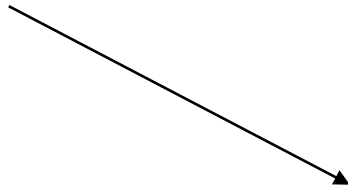
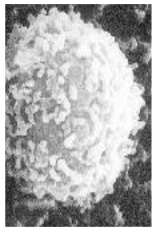
HIV RESISTANCE TO ART

Lessons from fundamental research

HIV RESISTANCE TO ART

Lessons from fundamental research

LESSON 1: THE HIV RESERVOIR IS MOSTLY DEFECTIVE



HIV-1 RESERVOIRS

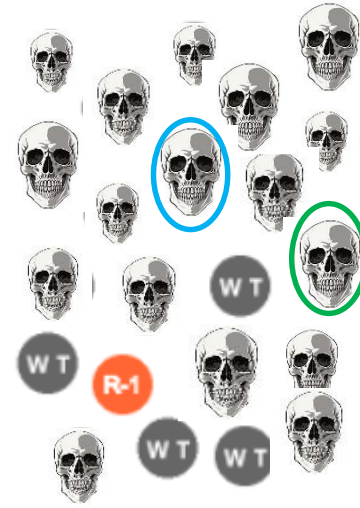
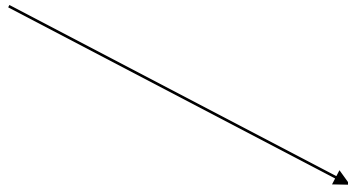
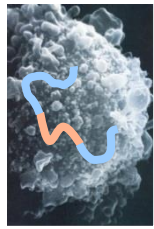
Latently-infected cells
rare event

Uninfected

Infected

CD4⁺ T lymphocytes

PROVIRUSES CARRYING DRM ARE MOSTLY DEFECTIVE



HIV-1 RESERVOIRS

Latently-infected cells
rare event

Uninfected

Infected

CD4⁺ T lymphocytes

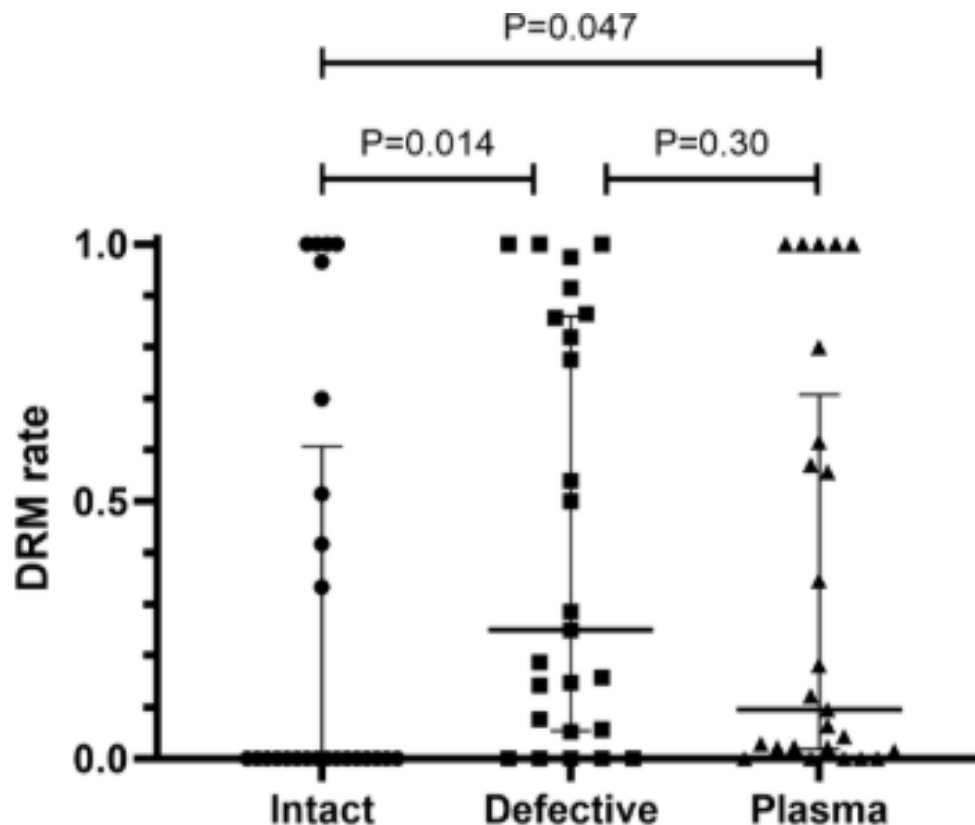
PROVIRUSES CARRYING DRM ARE MOSTLY DEFECTIVE

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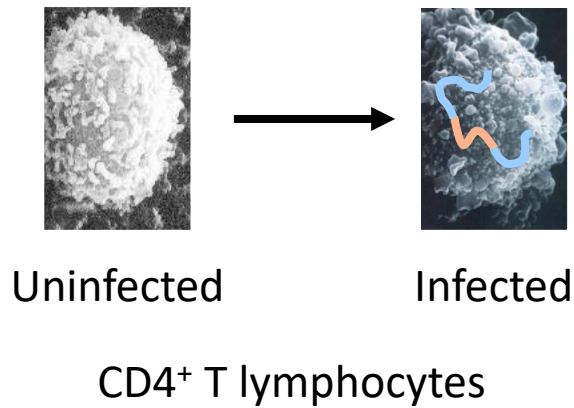
AIDS. 2021 June 01; 35(7): 1015–1020. doi:10.1097/QAD.0000000000002850.

Drug Resistance Mutations in HIV Provirus are Associated with Defective Proviral Genomes with Hypermutation

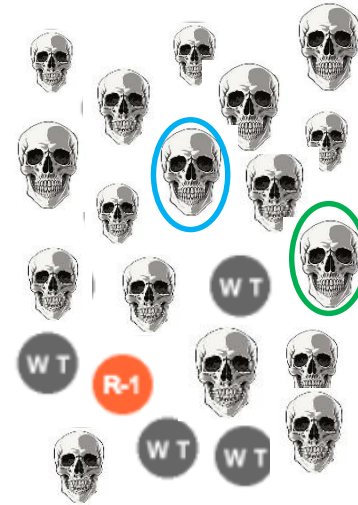
Yijia Li¹, Behzad Etemad¹, Ruth Dele-Oni², Radwa Sharaf¹, Ce Gao³, Mathias Lichterfeld^{1,3}, Jonathan Z Li¹



LESSONS 2: HIV RESERVOIRS ARE DYNAMIC



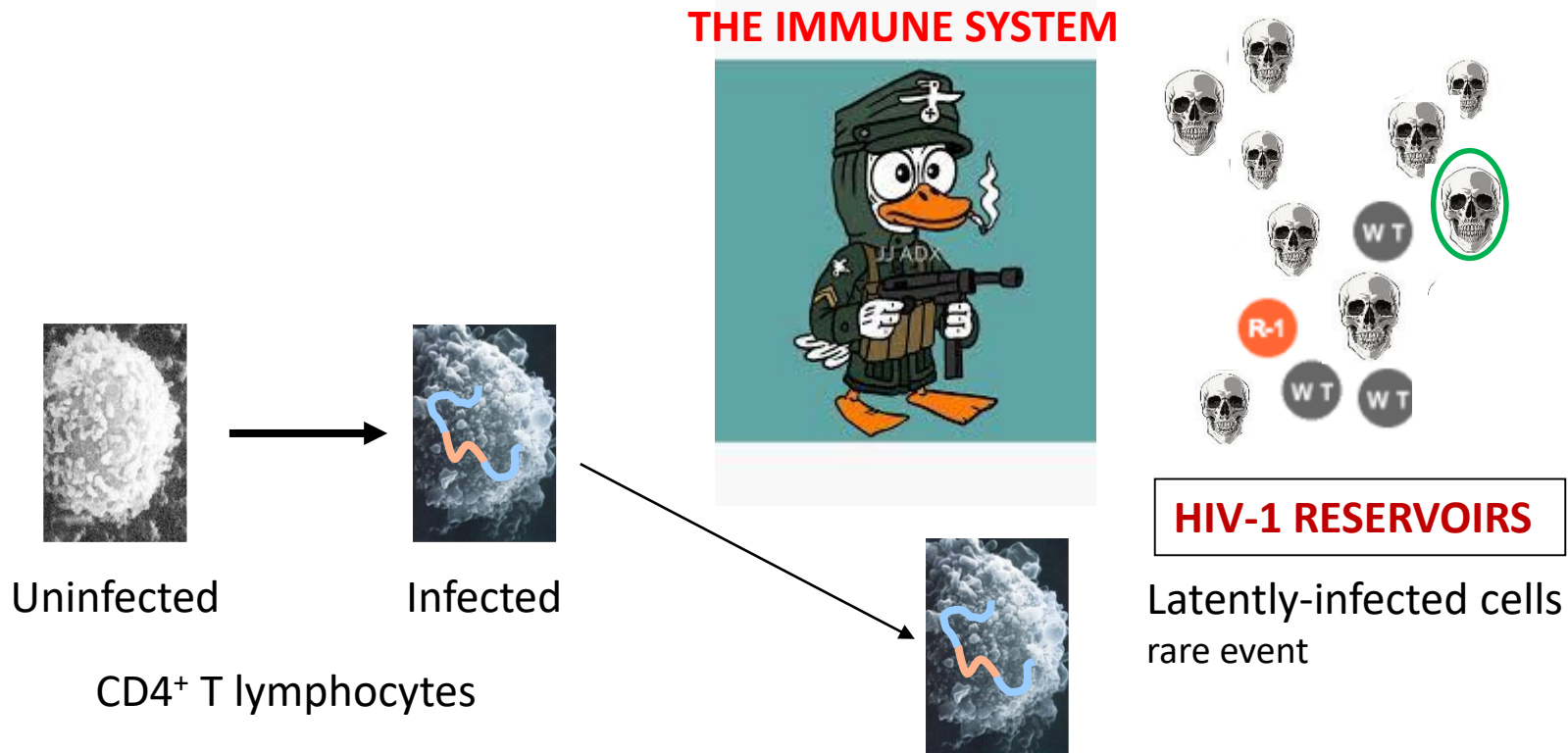
THE IMMUNE SYSTEM



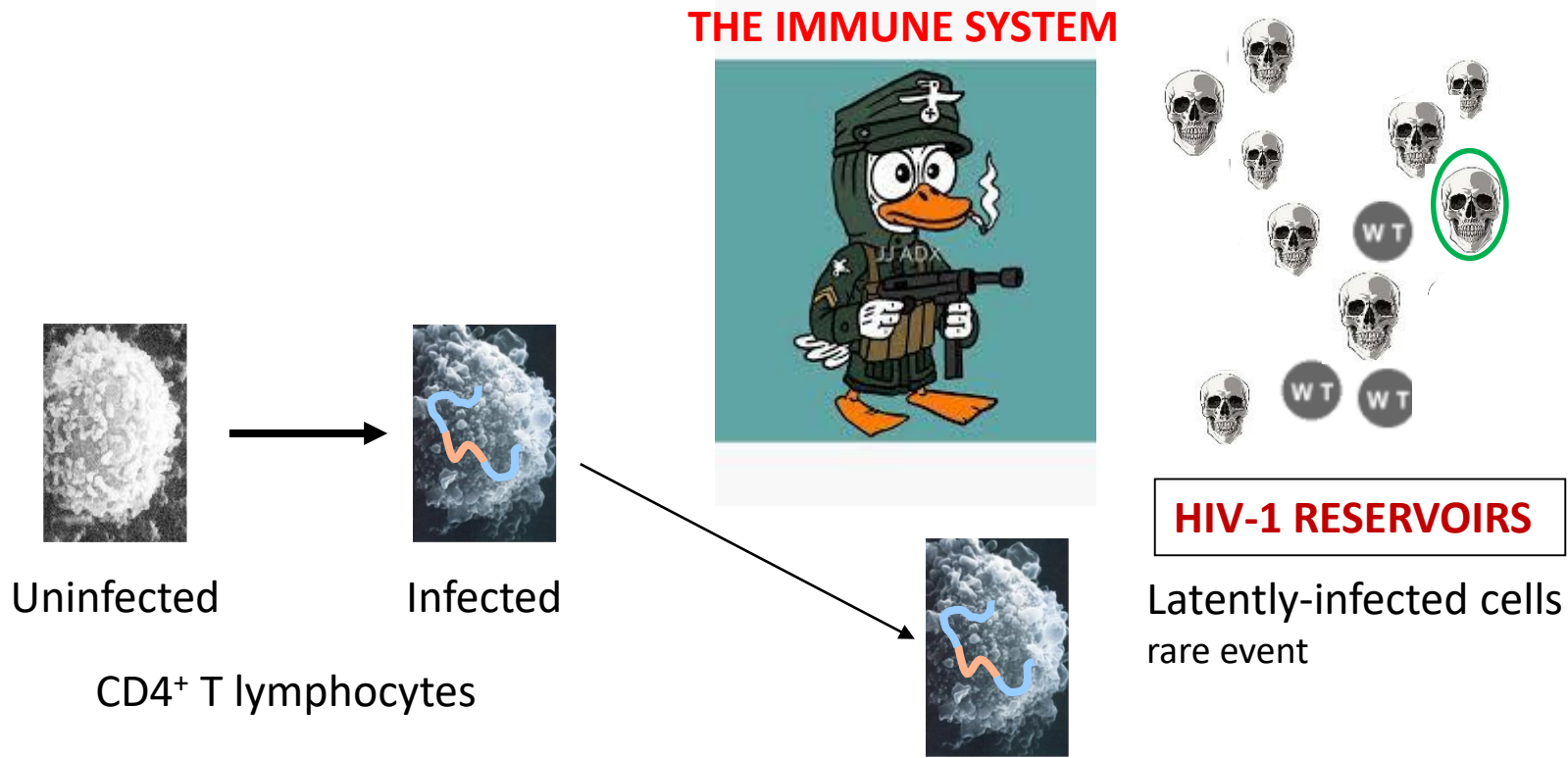
HIV-1 RESERVOIRS

Latently-infected cells
rare event

THE HIV RESERVOIR IS BEING RESHAPED BY THE IS



THE HIV RESERVOIR IS BEING RESHAPED BY THE IS



Decrease in overall reservoir complexity (and size)

LESSONS 2: PROVIRUSES CARRYING DRM MAY DISAPPEAR

The Journal of Infectious Diseases

MAJOR ARTICLE



Kinetics of Archived M184V Mutation in Treatment-Experienced Virally Suppressed HIV-Infected Patients

Romain Palich,^{1,2} Elisa Teyssou,² Sophie Sayon,² Basma Abdi,² Cathia Soulie,² Lise Cuzin,^{3,4} Roland Tubiana,¹ Marc-Antoine Valantin,¹ Luminita Schneider,¹ Sophie Seang,¹ Marc Wirden,² Valérie Pourcher,^{1,5} Christine Katlama,¹ Vincent Calvez,² and Anne-Genevieve Marcelin²

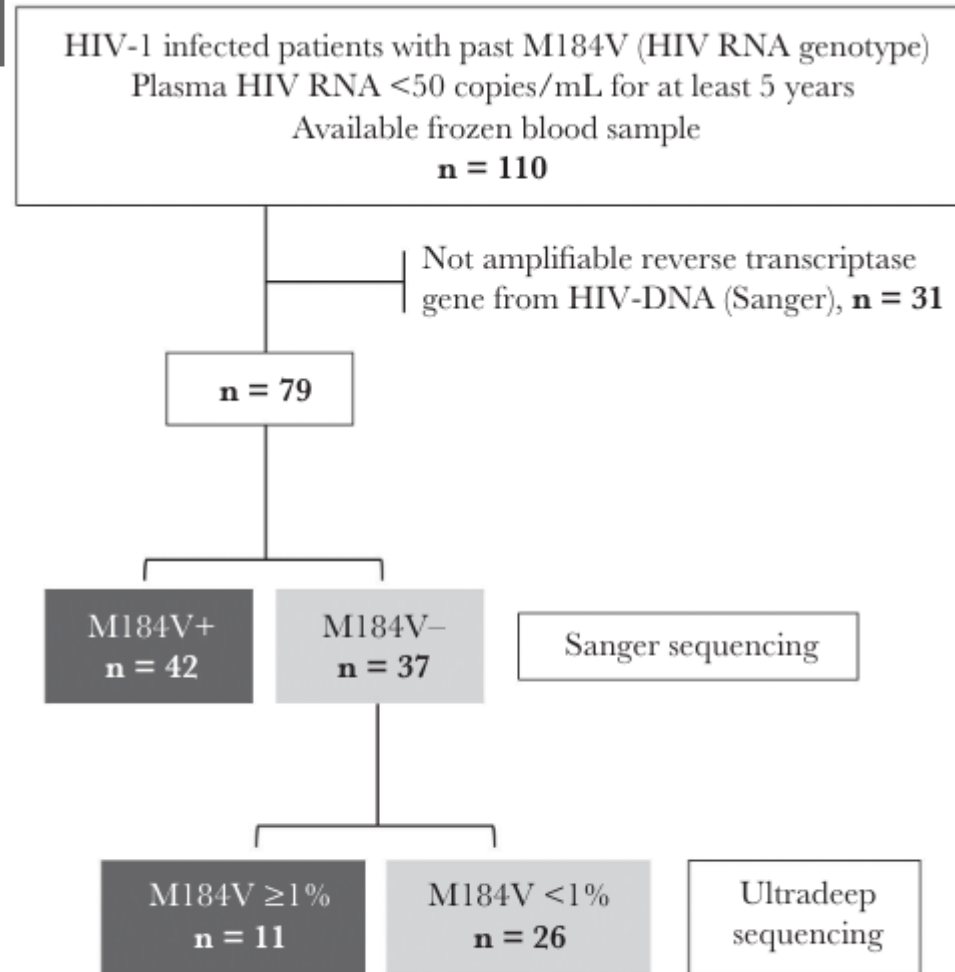


Figure 1. Study flowchart.

LESSONS 2: PROVIRUSES CARRYING DRM MAY DISAPPEAR

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mononuclear cells over time if the ART regimen excluded these drugs [13]. Our study supports the progressive decrease in the M184V mutation over time, with a kinetic not affected by the therapeutic pressure of 3TC/FTC. Eleven of 26 (42%) patients

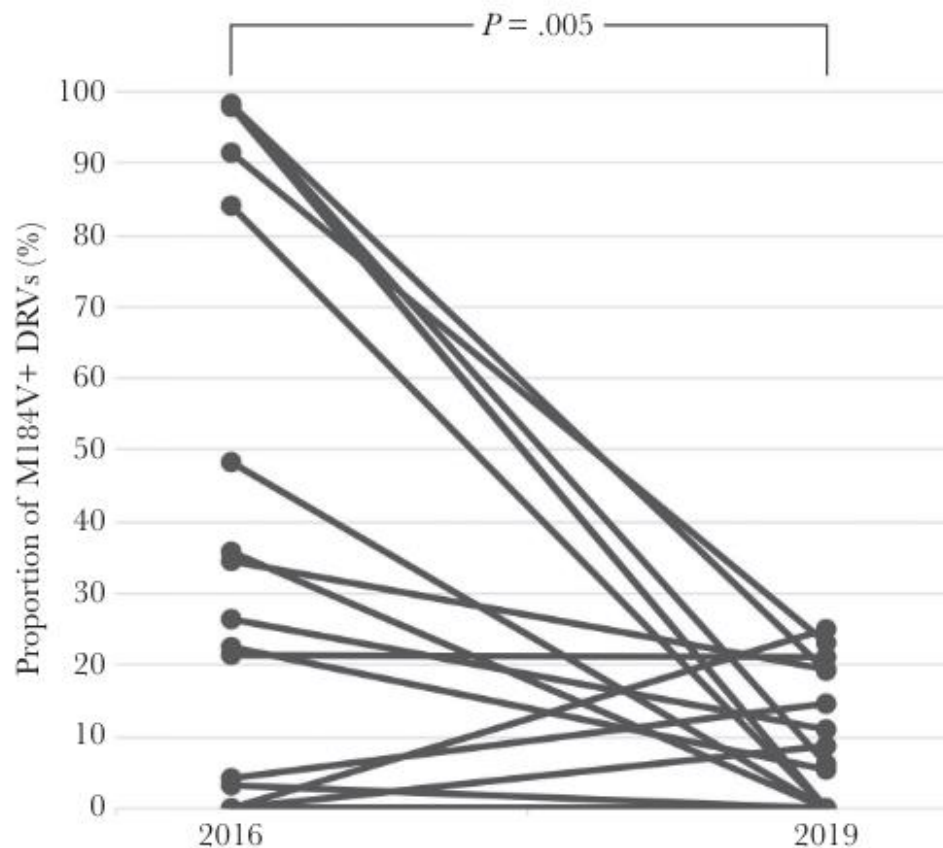


Figure 2. Proportion of drug-resistant viral variants (DRVs) carrying the M184V mutation in blood HIV DNA in 2016 and 2019. Each line represents 1 patient. Analysis by Student paired *t* test.

CONCLUSION

- **HIV resistance is considered cumulative because HIV carrying DRM persist in the reservoir**
- **HIV reservoirs are dynamic, intact proviruses being more rapidly eliminated**
- **Reservoirs simplification may lead to progressive elimination of proviruses carrying DRM**
- **The development of sensitive assay to analyse the reservoir are needed, not only from a cure perspective**

Thank you for your attention