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Introduction to the translational Research platform RegaVir

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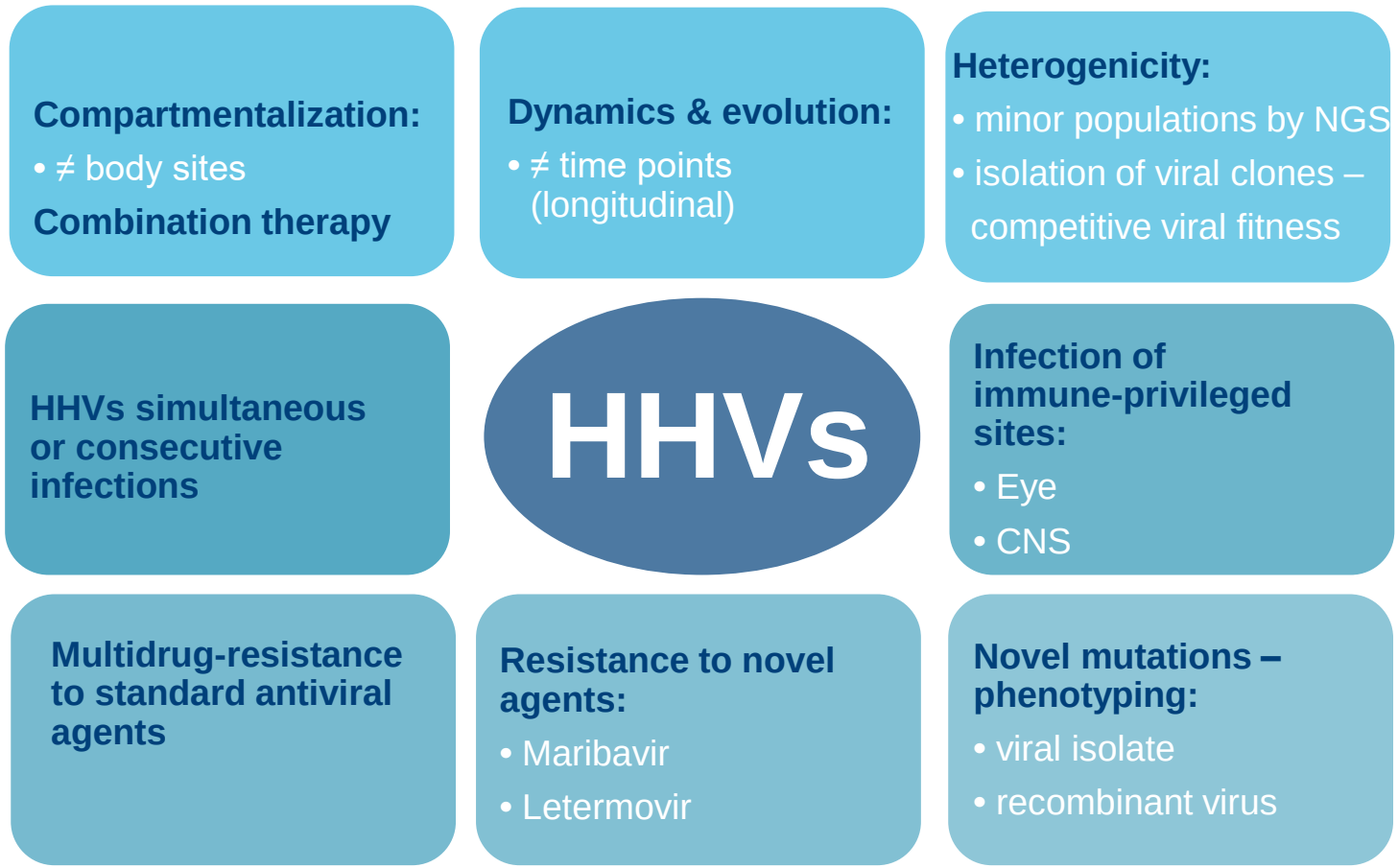
Leuven, January 30, 2024

RegaVir platform for translational research



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HSV infections

- Herpes simplex virus (HSV) infections are ubiquitous globally.

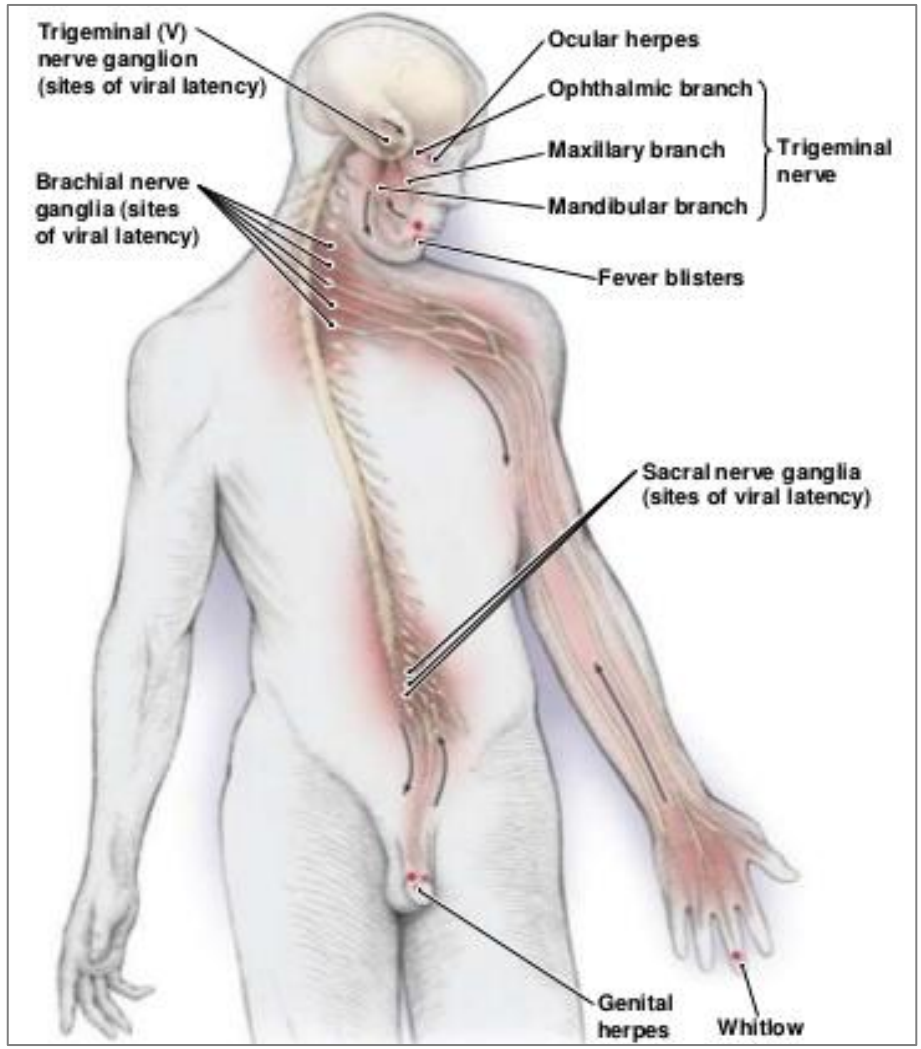
- **An estimated 3.7 billion people under age 50 (67%) globally have herpes simplex virus 1 (HSV-1) infection, the main cause of oral herpes.**

- **An estimated 491 million people aged 15–49 (13%) worldwide have herpes simplex virus 2 (HSV-2) infection, the main cause of genital herpes.**

HSV infections

- After a primary infection, HSV remains latently in sensory ganglia with the potential to reactivate.

- Most HSV infections are asymptomatic or unrecognized, but symptoms of herpes include painful blisters or ulcers that can recur over time.



HSV infections

- In immunocompromised individuals, **antiviral prophylaxis with acyclovir (ACV)** may be effective at preventing reactivation.

- Routine use of ACV prophylaxis has led to a **reduction in the incidence of early reactivation of HSV** after allogeneic bone marrow transplant.

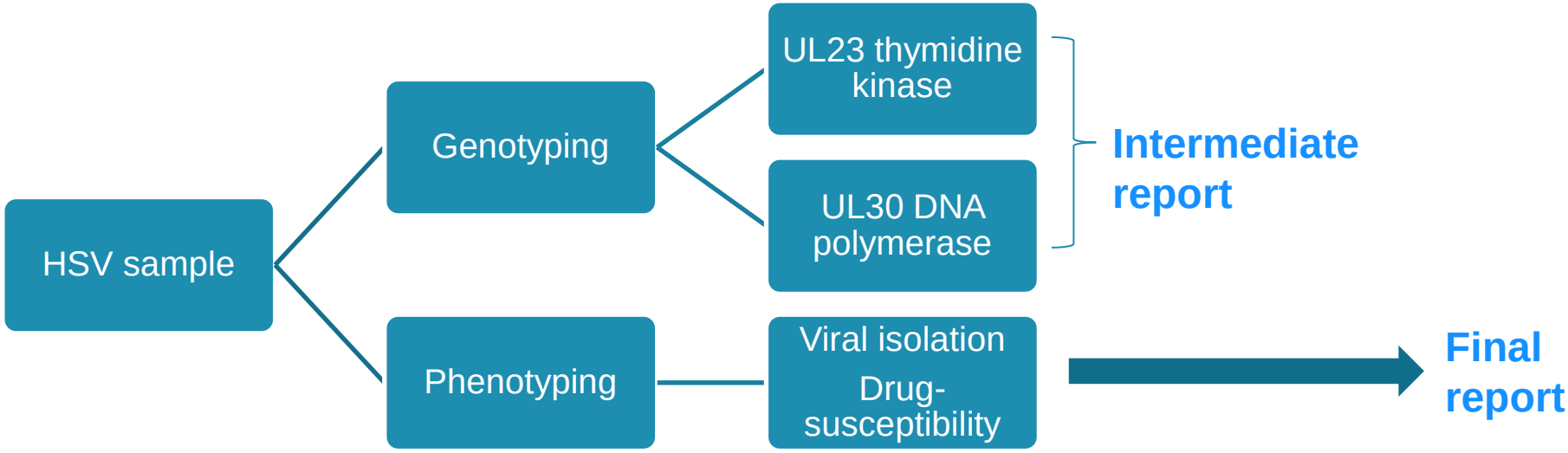
- **ACV is the most used drug for HSV infection therapy.**

Emergence of resistance to new anti-HCMV agents in a pediatric HSCT patient with IEI

- **Emergence of ACV-resistance (ACV-R)** has been increasingly reported and is associated with long-term ACV prophylaxis or therapy in immunocompromised patients.

- Due to the high polymorphism in genes involved in drug resistance, **phenotypic methods**, although work-intensive, are still required to test drug susceptibility.

RegaVir HSV workflow



- Phenotyping not done for CSF, ocular, and blood/plasma samples.
- **Swabs in UTM required for viral isolation (please, do not use eSwabs)**
- Between January 2009 and January 2024, **230 HSV-2 samples** were analyzed by RegaVir.

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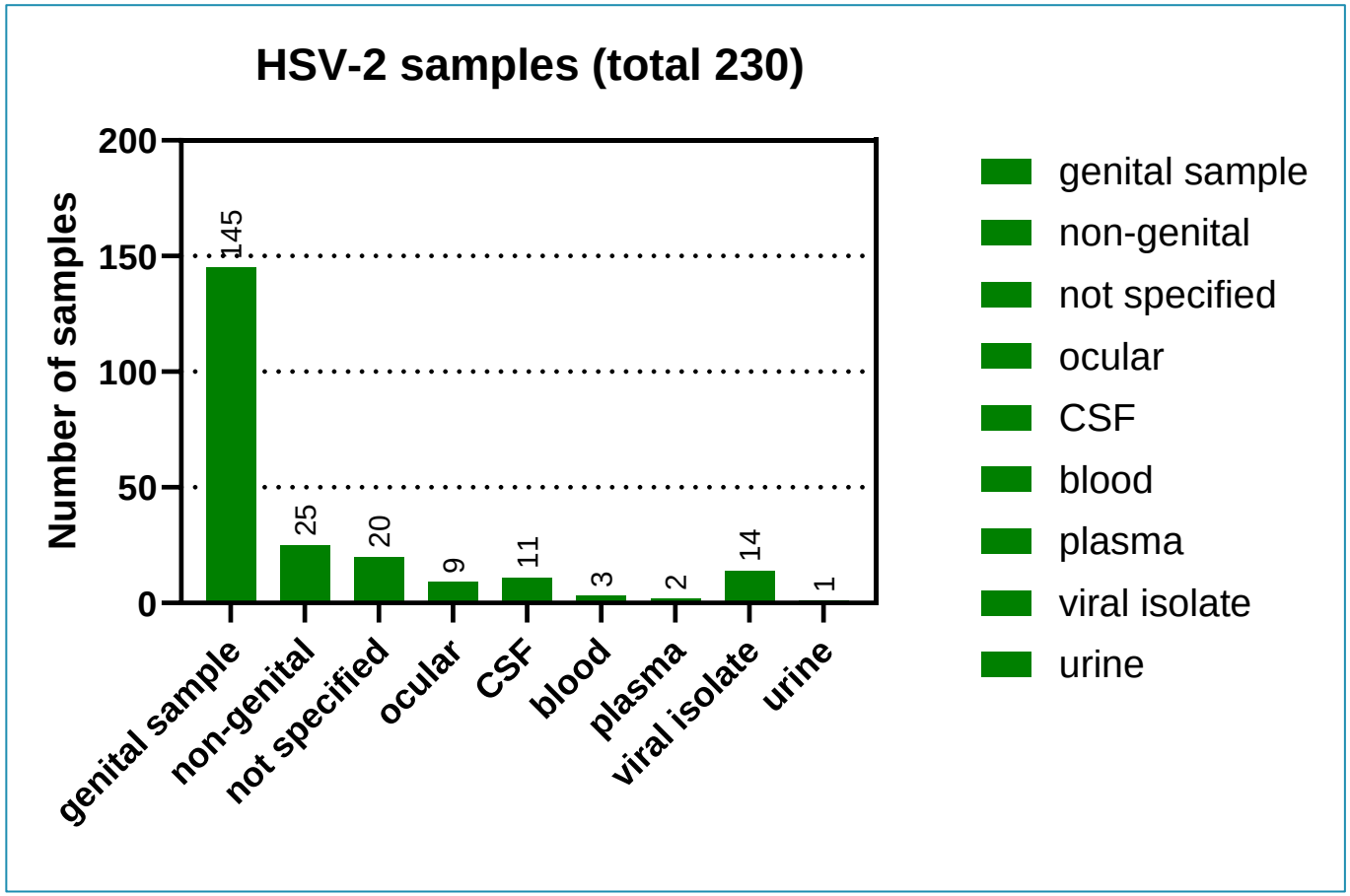
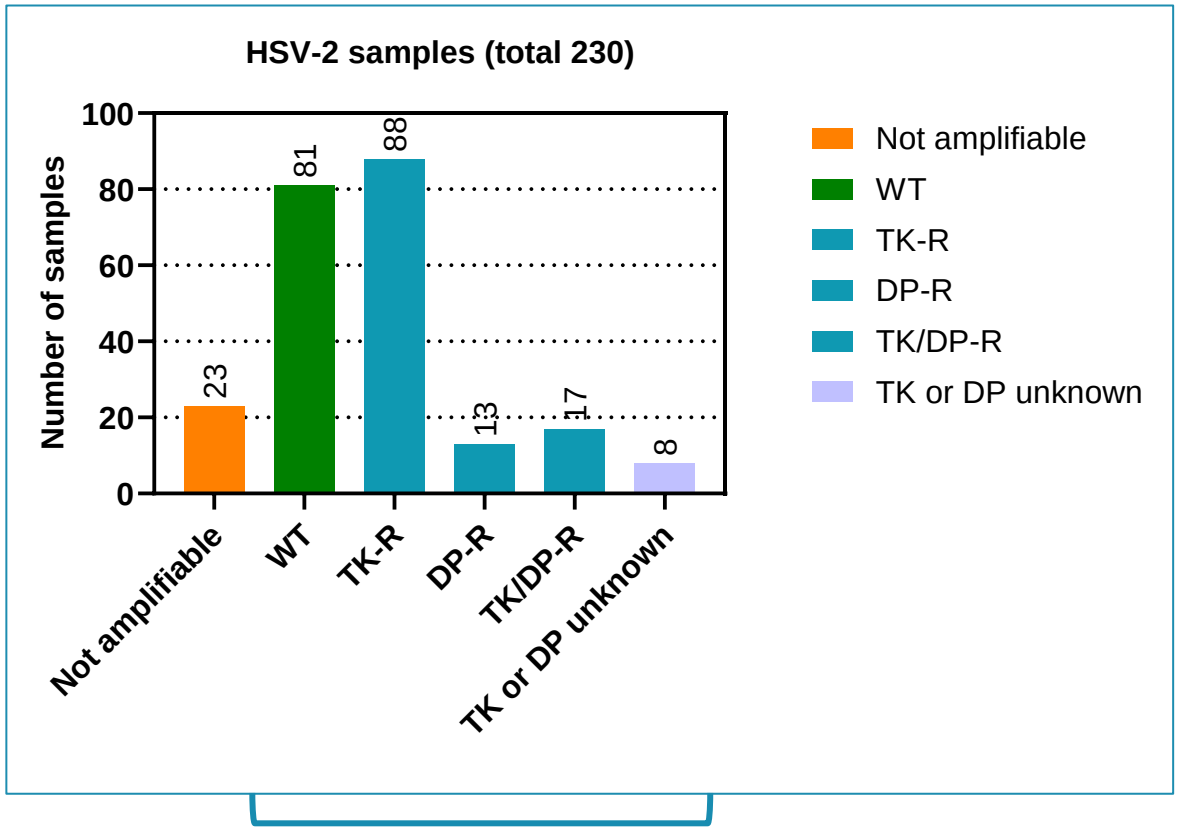
HSV-2 sample type



HSV-2 resistance samples



207 amplifiable samples . 230: 90%

118 confirmed resistance . 207 amplifiable samples: 57%

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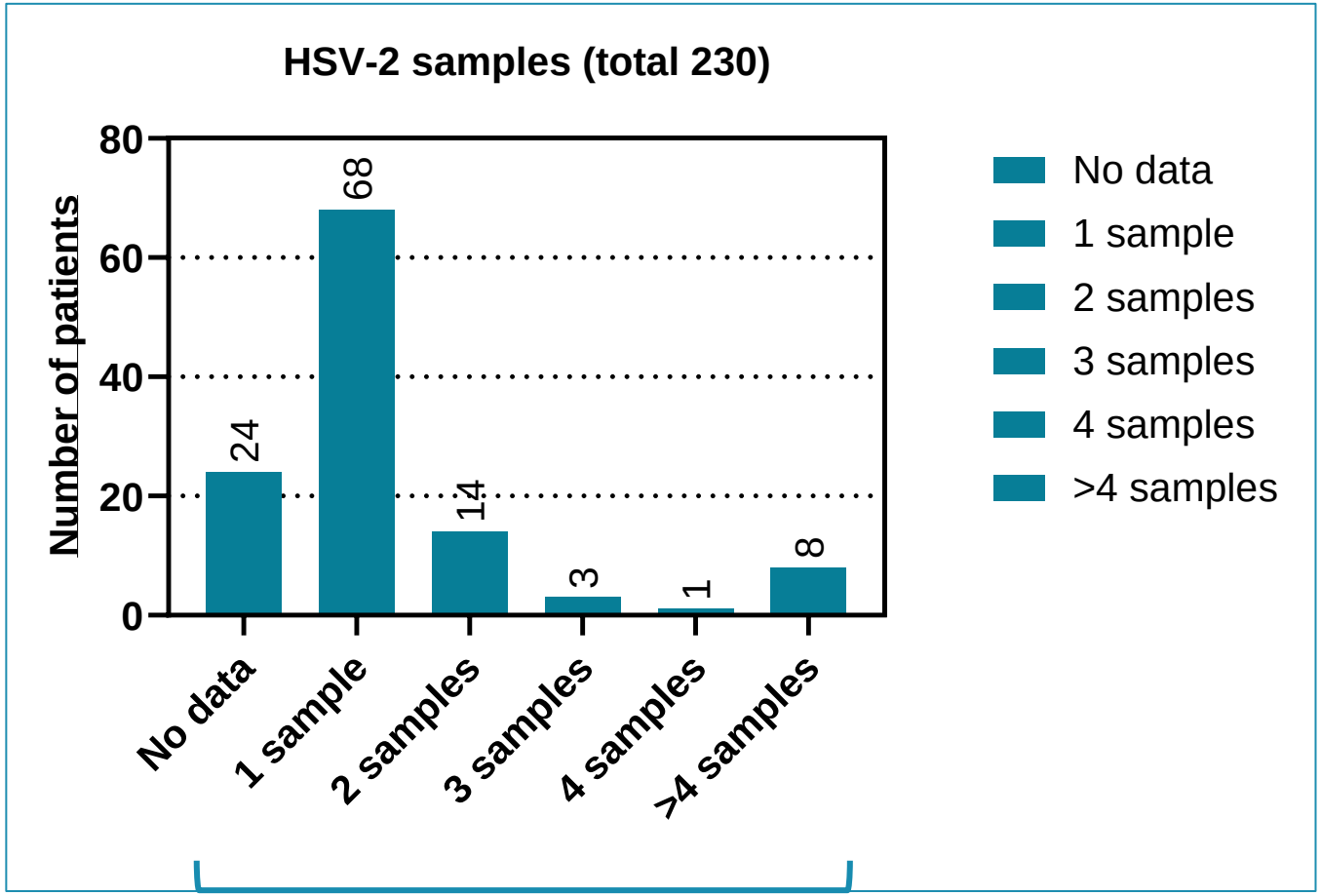
Patients analyzed for HSV-2



HSV-2 anogenital infections in HIV positive patients

- 77-years old men with recurrent anogenital HSV-2
- HIV positive
- Anogenital swabs recovred over 7 years

Date of arrival	RegaVir ID	Genotyping		Phenotyping
		TK	DNA pol	
06.04.09	RV_11	**C insertion nts 551-556 (6C's → 7 C's)**	Natural polymorphisms: S15P, P60L, P801T, G904A, E905A, A906G	**TK-resistance**
13.10.11	RV_257	**C deletion Nt 306 leading to a framshift mutation (truncated protein at amino acid 101)**	Natural polymorphisms: S15P, P60L, P801T, G904A, E905A, A906G	**TK-resistance**
01.04.10	RV_101	**C insertion nts 551-556 (6C's → 7 C's)**	Natural polymorphisms: S15P, P60L, P801T, G904A, E905A, A906G	**TK-resistance**
19.09. 14	RV_718	**C deletion Nt 306 leading to a framshift mutation (truncated protein at amino acid 101)**	Natural polymorphisms*: P801T, G904A, E905A, A906G	**TK-resistance**
28.04.16	RV_988	**C insertion nts 551-556 (6C's → 7 C's)**	Natural polymorphisms*: P801T, G904A, E905A, A906G	**TK-resistance**
19.10.16	RV_1078	**C deletion Nt 306 leading to a framshift mutation (truncated protein at amino acid 101)**	Natural polymorphisms: S15P, P60L, P801T, G904A, E905A, A906G	**TK-resistance**

*Partial sequence but all known drug-R mutations verified

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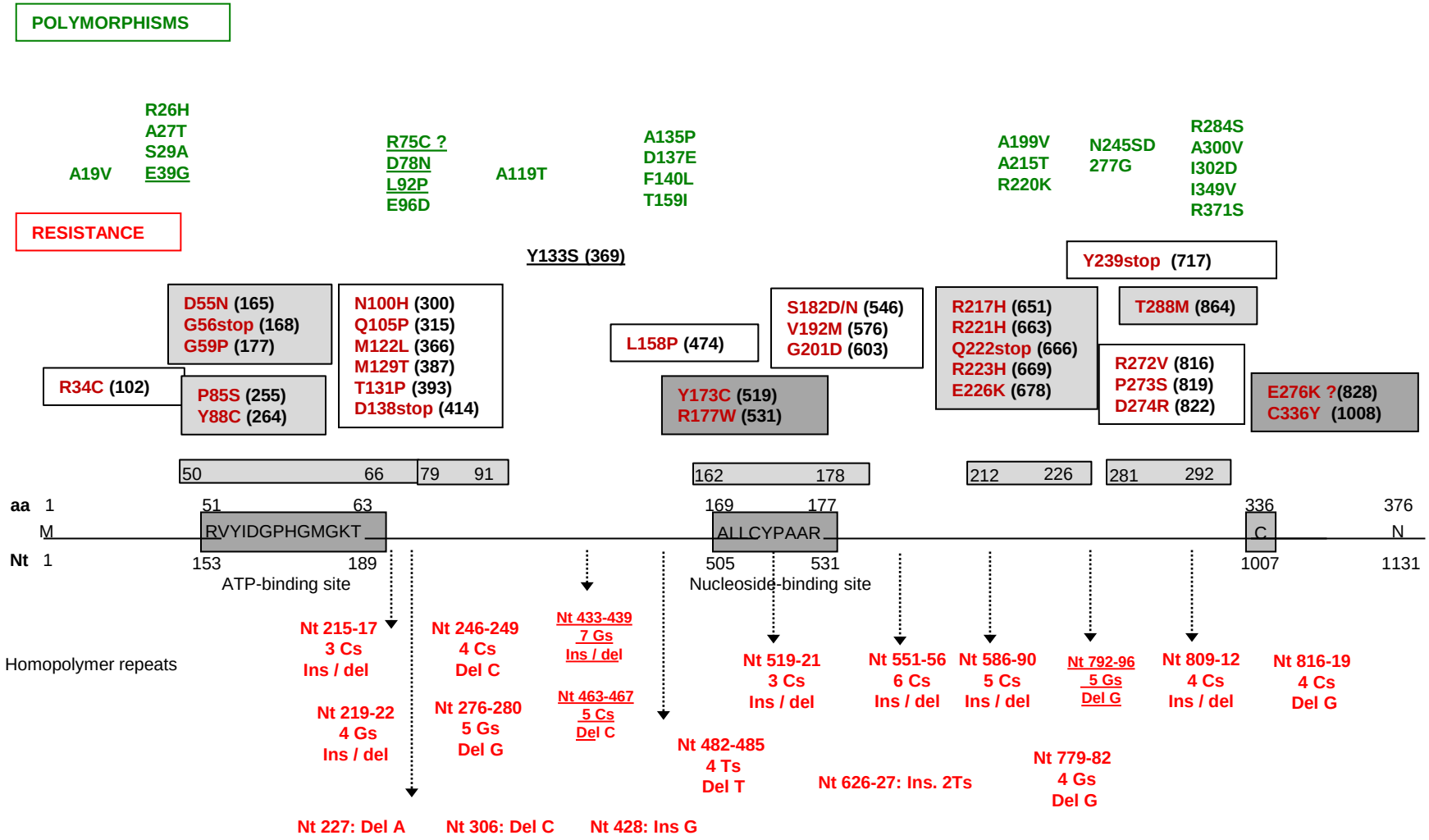
HSV-2 Thymidine kinase



Mutations previously described that are known to be associated with genetic polymorphism are indicated in green while those known to confer drug-resistance are marked in red. Mutations that confer drug resistance located in the ATP-binding site, the nucleoside-binding site, and Cys-336 are shown in dark grey boxes. Mutations found in other conserved regions of the viral TK are shown in pale grey boxes, and mutations located in non-conserved regions of the viral enzyme are shown in white boxes.
Mutations found in HSV-2 clinical isolates received during the RegaVir project are underlined , being the novel mutations associated with drug-resistance in a purple box.

Phenotyping in human embryonic lung fibroblasts

Strain	EC_{50} (µg/ml)						
	Acyclovir	Penciclovir	Brivudin	Ganciclovir	Foscavir	Cidofovir	Adefovir
RV-988	**12.63** **20**	**12.63** **20**	**>10** **>10**	**3.42** **2.99**	14.63 1956	0.8 0.8	20.07 30.59
Reference HSV-2 (G strain)	0.023	0.16	>10	0.0019	13.68	0.47	13.68
RV-1078	**6.84** **20**	**5.98** **12.63**	4.47 5.25	**1.45** **1.05**	3.58 5.8	0.42 0.39	10.46 13.68
Reference HSV-2 (G strain)	0.06	0.16	>10	0.0055	10.46	0.8	16.36
EC_{50} : Concentration required to reduce virus induced cytopathicity by 50%							

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HSV-2 infections in HIV positive patients

- ~70% of persons with HIV are HSV-2 seropositive.
- ~95% of persons with HIV are seropositive for either HSV-1 or HSV-2.

- HSV-2 infection increases the risk of HIV acquisition 2- to 3-fold.

- In coinfected patients, HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions.

- **Sexual transmission of HSV most often occurs during episodes of asymptomatic viral shedding.**

- Treatment failure due to acyclovir resistance should be suspected if herpes-related lesions do not begin to resolve within 7 days to 10 days after initiation of anti-HSV therapy.
- High prevalence of ACV-R HSV-2 in HIV positive patients unresponsive to therapy.

HSV-2 ocular infection (UZ Gent)

- 46-years old woman with intra-ocular HSV infection (08.12.2021)

- No predisposition, no immunosuppression

- Antiviral treatment received: prophylactic – therapeutic (in case of acute infection)
  - **Acyclovir**
    (08.12.2021 10 mg.kg 3x.day IV)
    (18.12.2021 *per os* 5x 800 mg.day)
  - **Foscarnet**
    intravitreal 2x.week (2.4 mg)

- Not improving under antiviral therapy - Increasing inflammation, retinal detachment

HSV-2 ocular infection (UZ Gent)

Arrival date to RegaVir	RegaVir ID	Sample date	Sample type	Viral load	HSV-2 genotype
03.01.2022	**RV-2408**	17.12.2021	DNA extract anterior chamber fluid	Ct = 27.4	**Wild-type** *DP natural polymorphisms: P801T, G904A, E905A, A906G*
03.01.2022	**RV-2409**	27.12.2021	DNA extract anterior chamber fluid	Ct = 25.8	**Wild-type** *DP natural polymorphisms: P801T, G904A, E905A, A906G*
25.01.2022	**RV-2421**	21.01.2022	DNA extract anterior chamber fluid	HSV-2 positive	**Wild-type** *DP natural polymorphisms: P801T, G904A, E905A, A906G*
07.02.2022	**RV-2432**	24.01.2022	DNA extract anterior chamber fluid	Ct = 29.65	**Wild-type** *DP natural polymorphisms: P801T, G904A, E905A, A906G*
07.02.2022	**RV-2433**	27.01.2022	DNA extract anterior chamber fluid	Ct = 30.15	**Wild-type** *DP natural polymorphisms: P801T, G904A, E905A, A906G*
07.02.2022	**RV-2434**	28.01.2022	DNA extract anterior chamber fluid	Ct = 27.97	**Wild-type** *DP natural polymorphisms: P801T, G904A, E905A, A906G*

Report 11.02.2022

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Ocular HSV-2 infection (Saint Luc – UCL Louvain)

- 24-years old woman
- Not immunosuppressed
- Ocular HSV infection
- Treatment not provided – in the last 10 days no treatment

Arrival date to RegaVir	RegaVir ID	Sample date	Sample type	Viral load	HSV-2 genotype
10.05.2022	**RV-2500**	10.05.2022	Anterior chamber fluid (right eye)	Not provided	**Wild-type** *TK natural polymorphism: G39E* *DP natural polymorphisms: P801T, G904A, E905A, A906G*

HSV-2 ocular infection (UZ Leuven)

- **29-years old man suffering from panuveitis (generalized inflammation of the whole uveal tract and also of the retina and vitreous humor) & papillitis (optic neuritis)** on the right eye (07.05.2018).
- Left eye same infection (panuveitis) in 2010 → vision light perception without localization.

- **Antiviral treatment:**
  - Therapeutic acyclovir IV 3x 300 mg (since 07/05//18)
  - Therapeutic foscarnet 0.1 cc intravitreal 3x (28/05/18, 31/05/18, 04/06/18)

- **Immunosuppressive treatment**
  - Medrol *per os*
  - Prednisolone forte (prednisolone acetate ophthalmic suspension) topical

HSV-2 ocular infection (UZ Leuven)

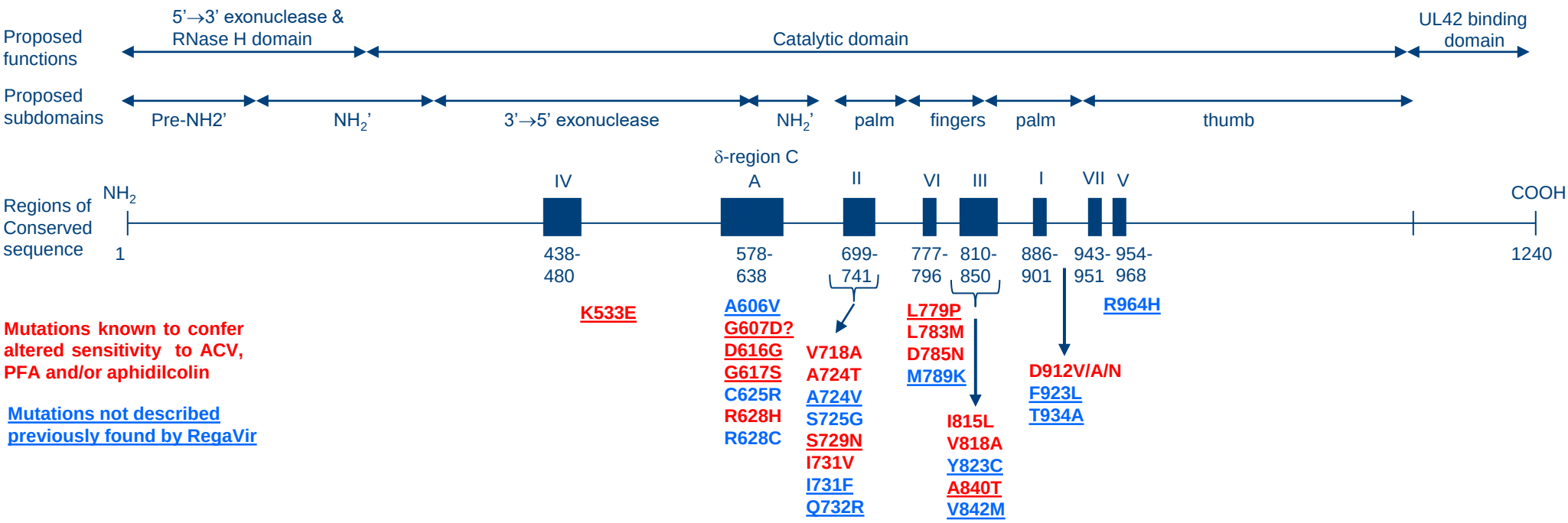
Arrival date to RegaVir	RegaVir ID	Sample date	Sample type	Viral load
29.05.2018	**RV-1472**	28.15.2018	Anterior chamber fluid	Not provided
12.06.2018	**RV-1484**	11.06.2018	Anterior chamber fluid	Not provided

	Mutations in the UL23 gene (thymidine kinase) (376 amino acids) Complete sequence		
	Related to genetic polymorphism (inter-strain variability)	**Known to be associated with resistance to antiviral agents**	**Novel of unknown significance**
RV-1472	G39E N78D **A317V (novel)** **V335I (novel)**	None	**P271T**
RV-1484	G39E N78D **A317V (novel)** **V335I (novel)**	None	**P271T**

	Amino acid changes in the UL30 (DNA polymerase) (1240 amino acids)	
	Known to be related to genetic polymorphism (inter-strain variability)	**Known to be associated with resistance to antiviral agents**
RV-1472 (partial sequence: amino acids 310-1240)	G646S A insertion 650-651 D667G* K674R EA insertion 677-678 D681A P801T G904A E905A A906G A977T* D985N* T987S* G990T* Q1013R* A1014E* G1016E* A1055P* V1088A* L1101H* A1105P* E1109D* PAPP deletion 1110-1113* L1116T* E1125P* P1127G* S1128A* H1129P* A1130R* D1131G* P1133E* G1135A* A1136G* S1137P*	None (all the positions verified)

* New polymorphisms

HSV-2 DNA polymerase



Mutations known to confer altered sensitivity to ACV, PFA and/or aphidilcolin

Mutations not described previously found by RegaVir

Genetic polymorphisms

M1R
A9T
P15S/R
Q43R
Q34H
P37L
R41S/H
H49Y
P60L

E139K
A232T
R265H
N286Y

G324E
L380P
A435V/T

G507H
Q571L
G631D
G646S
R654C
G660E
D671N
K674R
D676N/G

E678G
G680R/D
D681A
E682K
V690A
Del DD (676-677)
Del DED (677-679)
Ins AE (679-680)
Del GD (681-682)
Del DGDE (683-686)
Ins DGDE (683-686)
Ins GGC (A) (650-651)

D716N
V748A
S777G
Q799R

T801P
P880H

Y856C
V857A/T
H858Y
A859T

T903M
A904G
A905E
G906A
I950L
L995F

A1000T
A1083T
I1026S

A1114V
D1131N
K1121E
E1149G
V1176A
A1223V

Del PGDEPA (1106-1111)

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	Amino acid changes in the UL30 (DNA polymerase) (1240 amino acids)	
	Known to be related to genetic polymorphism (inter-strain variability)	**Known to be associated with resistance to antiviral agents**
RV-1484 partial sequence: amino acids 310-1068 * New polymorphisms	G646S A insertion 650-651 D667G* K674R EA insertion 677-678 D681A P801T G904A E905A A906G A977T* D985N* T987S* G990T* Q1013R* A1014E* G1016E* A1055P*	**None (all the positions verified)**

HSV-2 genital infection (UZ Gent)

- 24-years old woman with painful and recurrent gluteal HSV-2 lesions

- Antiviral treatment:
  - Valacyclovir daily 2x 500mg for 6 years
  - During exacerbations 3x 1g daily

Arrival date to RegaVir	RegaVir ID	Sample date	Sample type	Viral load
21.04.2016	**RV-983**	15.04.2016	Genital sample (vesicular fluid)	Not provided

HSV-2 genital infection (UZ Gent)

- 24-years old woman with painful and recurrent gluteal HSV-2 lesions

- Antiviral treatment:
  - Valacyclovir daily 2x 500mg for 6 years
  - During exacerbations 3x 1g daily

	Mutations in the UL23 gene (thymidine kinase) (376 amino acids) Complete sequence	
	Known to be related to genetic polymorphism (inter-strain variability)	**Known to be associated with resistance to antiviral agents**
RV-1472	G39E N78D	None (all positions verified)

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	Amino acid changes in the UL30 (DNA polymerase) (1240 amino acids)		
	Known to be related to genetic polymorphism (inter-strain variability)	**Novel**	**Known to be associated with resistance to antiviral agents**
RV-983 (partial sequence: amino acids 309-1240)	D676G P801T G904A E905A A906G	A977T D985N T987S G990T Q1013R A1014E G1016E A1055P V1088A L1101H A1105P E1109D Deletion PAPP (1110-1113) L1116T E1125P P1127G S1128A H1129P A1130R D1131G P1133E G1135A A1136G	**None (all the positions could be verified)**

HSV-2 genital infection (UZ Gent)

Strain	EC_{50} (µg.ml)						
	Acyclovir	Penciclovir	Brivudin	Ganciclovir	Foscavir	Cidofovir	Adefovir
RV-983	0.024 0.032	0.072 0.064	>10 10	0.0023 0.0025	25.26 25.26	1.2 1.1	21.87 21.87
Reference HSV-2 (G strain)	0.024	0.024	>10	0.00096	21.87	0.3	8.0
EC_{50} : Concentration required to reduce virus induced cytopathicity by 50% in HEL cells.							

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HSV-2 genital infection (UZ Leuven)

- 66-years old woman with anogenital HSV-2 infection (sacro-anal)

- Not immunosuppressed

- Antiviral treatment:
  - Prophylactic valacyclovir 3x 1000 mg/day – cyclic, not continuous
  - Patient under self-medication taking high valacyclovir doses during several years

HSV-2 genital infection (UZ Leuven)

Arrival date to RegaVir	RegaVir ID	Sample date	Sample type	Viral load
22.06.2023	**RV-2760**	21.06.2023	Anogenital swab	Not provided
29.06.2023	**RV-2765**	28.06.2023	Anogenital swab	Not provided

	Mutations in the UL23 gene (thymidine kinase) (376 amino acids) Complete sequence		
	Known to be related to genetic polymorphism (inter-strain variability)	**Known to be associated with resistance to antiviral agents**	**Novel of unknown significance**
RV-2760	G39E N78D	None	**P273L (P273S as a drug-R mutation) + E276K**
RV-2765	G39E N78D	None	**P273L (P273S as a drug-R mutation) + E276K**

	Amino acid changes in the UL30 (DNA polymerase) (1240 amino acids)		
	Known to be related to genetic polymorphism (inter-strain variability)	**Novel**	**Known to be associated with resistance to antiviral agents**
RV-2760 (complete sequence)	A435T G646S A651ins D667G K674R AE679-680ins D681A P801T G904A E905A A906G	A9T T53A T144P A977T D985N T987S G990T Q1013R A1014E G1016E A1055P V1088A L1101H A1105P E1109D PAPP1110-1113del L1116T E1125P P1127G S1128A H1129P A1130R D1131G P1133E G1135A A1136G S1137P	**None (all the positions could be verified)**

	Amino acid changes in the UL30 (DNA polymerase) (1240 amino acids)		
	Known to be related to genetic polymorphism (inter-strain variability)	**Novel**	**Known to be associated with resistance to antiviral agents**
RV-2765 (complete sequence)	A435T G646S D667G K674R AE679-680ins D681A P801T G904A E905A A906G	A9T T53A T144P A977T D985N T987S G990T Q1013R A1014E G1016E A1055P V1088A L1101H A1105P E1109D PAPP1110-1113del L1116T E1125P P1127G S1128A H1129P A1130R D1131G P1133E G1135A A1136G S1137P	**None (all the positions could be verified)**

HSV-2 genital infection (UZ Leuven)

Strain	EC_{50} (µg.ml)								
	Acyclovir	Penciclovir	Brivudin	Ganciclovir	Foscavir	Cidofovir	Adefovir	Trifluridine	Pritelivir
Reference HSV-2 (G strain)	0.068 0.054 0.068	0.094 0.057 0.12	>10 >10 4.89	0.0072 0.0021 0.013	23.39 20.62 27.59	0.22 0.37 0.44	5.35 10.46 16.36	2.99 2.0 4.47	0.0032 0.016 0.029
Mean	0.063	0.090	≥ 8.3	0.007	23.867	0.343	10.723	3.153	0.016
RV-2760	0.032 0.065 0.051 0.042	0.21 0.10 0.075 0.12	>10.0 >10.0 2.0	0.012 0.032 0.0083 0.012	25.26 52.31 23.39 25.26	0.55 1.62 0.55 0.55	11.6 19.03 4.37	3.28 4.09 0.84 0.89	0.025 0.030 0.0088 0.023
Mean	0.048	0.13	≥ 7.33	0.016	31.56	0.82	11.67	2.28	0.022
Fold resistance	0.8	1.4	0.9	2.2	1.3	2.4	1.1	0.7	1.4

EC_{50}: Concentration required to reduce virus induced cytopathicity by 50%
Fold resistance (EC_{50} sample.EC_{50} G strain)

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Alignment of the DNA polymerase

HSV-2 lab strains

HSV-2 RegaVir isolates

HSV-2 isolates with high DNA pol variability

HSV-2 variant (HSV-2v) isolates

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HSV-2_HG52          AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRGLDKE-APKRPAVPR    659
HSV-2_G             AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRGLDKE-APKRPAVPR    659
HSV-2_RV-2514       AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRGLDKE-APKRPAVPR    659
HSV-2_RV-2726       AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRGLDKE-APKRPAVPR    659
HSV-2_RV-2852       AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRGLDKE-APKRPAVPR    659
HSV-2v_RV-983       AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRGLDKE-APKRPAVPR    659
HSV-2v_RV-2760      AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRSLDKEAAPKRPAVPR    660
HSV-2v_RV-2765      AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRSLDKE-APKRPAVPR    659
HSV-2v_RV-1472      AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRSLDKEAAPKRPAVPR    351
HSV-2v_RV-1484      AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRSLDKEAAPKRPAVPR    351
HSV-2v_pat1         AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRSLDKEAAPKRPAVPR    660
HSV-2v_pat2         AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRSLAKEAAPKRPAVPR    660
HSV-2v_pat3         AVARLAGINITRTIYDGQQIRVFTCLLRLAGQKGFILPDTQGRFRSLDKEAAPKRPAVPR    660
                    ********************************************.* ** *********

HSV-2_HG52          GEGERPGDGNGDEDKDDD--EDGDEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    717
HSV-2_G             GEGERPGDGNGDEDKDDD--EDGDEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    717
HSV-2_RV-2514       GEGERPGDGNGDEDKDDD--EDGDEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    717
HSV-2_RV-2726       GEGERPGDGNGDEDKDDD--GDGDEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    717
HSV-2_RV-2852       GEGERPGDGNGDEDKDDD--EDGDEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    717
HSV-2v_RV-983       GEGERPGDGNGDEDKDGD--EDGDEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    717
HSV-2v_RV-2760      GEGERPGGGNGDEDRDDDEAEDGAEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    720
HSV-2v_RV-2765      GEGERPGGGNGDEDRDDDEAEDGAEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    719
HSV-2v_RV-1472      GEGERPGGGNGDEDRDDDEAEDGAEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    411
HSV-2v_RV-1484      GEGERPGGGNGDEDRDDDEAEDGAEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    411
HSV-2v_pat1         GEGERPGGGNGDEDRDDDEAEDGAEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    720
HSV-2v_pat2         GEGERPGGGNGDEDRDDDEAEDGAEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    720
HSV-2v_pat3         GEGERPGGGNGDEDRDDDEAEDGAEDGDEREEVARETGGRHVGYQGARVLDPTSGFHVDP    720
                    *******.******:*.*   ** **********************************
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HSV-2_HG52          KGVDLVRKNNCAFINRTSRALVDLLFYDDTVSGAAAALAERPAEEWLARPLPEGLQAFGA    1017
HSV-2_G             KGVDLVRKNNCAFINRTSRALVDLLFYDDTVSGAAAALAERPAEEWLARPLPEGLQAFGA    1017
HSV-2_RV-2514       KGVDLVRKNNCAFINRTSRALVDLLFYDDTVSGAAAALAERPAEEWLARPLPEGLQAFGA    1017
HSV-2_RV-2726       KGVDLVRKNNCAFINRTSRALVDLLFYDDTVSGAAAALAERPAEEWLARPLPEGLQAFGA    1017
HSV-2_RV-2852       KGVDLVRKNNCAFINRTSRALVDLLFYDDTVSGAAAALAERPAEEWLARPLPEGLQAFGA    1017
HSV-2v_RV-983       KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    1017
HSV-2v_RV-2760      KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    1020
HSV-2v_RV-2765      KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    1019
HSV-2v_RV-1472      KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    711
HSV-2v_RV-1484      KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    711
HSV-2v_pat1         KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    1020
HSV-2v_pat2         KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    1020
HSV-2v_pat3         KGVDLVRKNNCAFINRTSRTLVDLLFYNDSVSTAAAALAERPAEEWLARPLPEGLREFEA    1020
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HSV-2_HG52          VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLAHLTVYYKLMARRAQVPSIKDRI    1077
HSV-2_G             VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLAHLTVYYKLMARRAQVPSIKDRI    1077
HSV-2_RV-2514       VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLAHLTVYYKLMARRAQVPSIKDRI    1077
HSV-2_RV-2726       VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLAHLTVYYKLMARRAQVPSIKDRI    1077
HSV-2_RV-2852       VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLAHLTVYYKLMARRAQVPSIKDRI    1077
HSV-2v_RV-983       VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMARRAQVPSIKDRI    1077
HSV-2v_RV-2760      VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMARRAQVPSIKDRI    1080
HSV-2v_RV-2765      VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMARRAQVPSIKDRI    1079
HSV-2v_RV-1472      VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMARRAQVPSIKDRI    771
HSV-2v_RV-1484      VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMA------------    759
HSV-2v_pat1         VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMARRAQVPSIKDRI    1080
HSV-2v_pat2         VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMARRAQVPSIKDRI    1080
HSV-2v_pat3         VLVDAHRRITDPERDIQDFVLTAELSRHPRAYTNKRLPHLTVYYKLMARRAQVPSIKDRI    1080
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HSV-2_HG52          PYVIVAQTREVEETVARLAALRELDAAAPGDEPAPPAALPSPAKRPRETPSHADPPGGAS    1137
HSV-2_G             PYVIVAQTREVEETVARLAALRELDAAAPGDEPAPPAALPSPAKRPRETPSHADPPGGAS    1137
HSV-2_RV-2514       PYVIVAQTREVEETVARLAALRELDAAAPGDEPAPPAALPSPAKRPRETPSHADPPGGAS    1137
HSV-2_RV-2726       PYVIVAQTREVEETVARLAALRELDAAAPGDEPAPPAALPSPAKRPRETPSHADPPGGAS    1137
HSV-2_RV-2852       PYVIVAQTREVEETVARLAALRELDAAAPGDEPAPPAALPSPAKRPRETPSHADPPGGAS    1137
HSV-2v_RV-983       PYVIVAQTREAEETVARLAALREHDAAPPGDDAA----TPSPAKRPRPTGAPRGPEGAGP    1133
HSV-2v_RV-2760      PYVIVAQTREAEETVARLAALREHDAAPPGDDAA----TPSPAKRPRPTGAPRGPEGAGP    1136
HSV-2v_RV-2765      PYVIVAQTREAEETVARLAALREHDAAPPGDDAA----TPSPAKRPRPTGAPRGPEGAGP    1135
HSV-2v_RV-1472      PYVIVAQTREAEETVARLAALREHDAAPPGDDAA----TPSPAKRPRPTGAPRGPEGAGP    827
HSV-2v_RV-1484      ------------------------------------------------------------    759
HSV-2v_pat1         PYVIVAQTREAEETVARLAALREHDAAPPGDDAA----TPSPAKRPRPTGAPRGPEGAGP    1136
HSV-2v_pat2         PYVIVAQTREAEETVARLAALREHDAAPPGDDAA----TPSPAKRPRPTGAPRGPEGAGP    1136
HSV-2v_pat3         PYVIVAQTREAEETVARLAALREHDAAPPGDDAA----TPSPAKRPRPTGAPRGPEGAGP    1136
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HSV-2 variant (HSV-2v)

- Both HSV-1 & HSV-2 species show overall **low levels of genomic variability**
- HSV-1 strains are generally more diverse than HSV-2 strains (mean pairwise distance of 0.8% for HSV-1 and 0.1% for HSV-2).

- In 2013, **a new HSV-2 variant (HSV-2v)** was identified in patients originating from West Africa, which showed an unexpectedly high variability (2.4% divergence) in the viral DNA pol.

- **HSV-2v** clearly differed from classical HSV-2 isolates in phylogenetic analyses and **may be linked to simian ChHV.**

- This new HSV-2 variant highlights the **possible occurrence of recombination between human and simian herpesviruses under natural conditions**, potentially presenting greater challenges for the future.

Ancient Recombination Events between Human Herpes Simplex Viruses

- Burrel et al , 201: WGS of 18 HSV-2 clinical isolates characterized by divergent UL30 gene sequences to further elucidate the evolutionary history of this virus.

- **Two main HSV-2 lineages exist:**
- One mostly restricted to subSaharan Africa
- One has reached a global distribution (only the worldwide lineage is characterized by ancient recombination events with HSV-1).

→ **Complexity of HSV-2 evolution**, a virus of putative zoonotic origin which later recombined with its human-adapted relative.

→ **Coinfections with HSV-1 and 2** may have genomic and potentially functional consequences and should therefore be monitored more closely.

Thank you for your attention

Any questions?

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