

REFRACTORY AND RESISTANT HSV INFECTIONS IN IMMUNOCOMPROMISED PATIENTS: SYSTEMATIC REVIEW AND PROPOSED DEFINITIONS

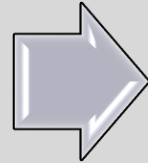
Tali Shafat, MD

Roy F Chemaly, MD, MPH

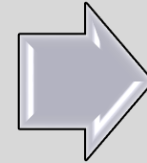
Department of Infectious Diseases, Infection Control, and Employee Health
The University of Texas MD Anderson Cancer Center
Houston Tx, USA

Introduction

Herpes simplex virus (HSV) infection is one of the most common viral infections worldwide



Prolonged use of antivirals in immunocompromised patients



Resistant strains emerged

HSV infections burden in USA

Seropositivity is **40-50%** in adults (2018)

20-25% are symptomatic with **orofacial or genital lesions**

Ocular disease annual incidence is **6.8 to 31 cases per 100,000**

Encephalitis annual incidence is **1 case per 100,000-150,000**

Pneumonitis, hepatitis – rare

HSV-1

Seropositivity is **10-15%** in those who are sexually active (2018)

10-15% are symptomatic with **anogenital lesions**

HSV-2

Resistance prevalence

**Up to 1% in
Immunocompetent
patients**

**Up to 3.5% in solid organ transplant
(SOT) recipients**

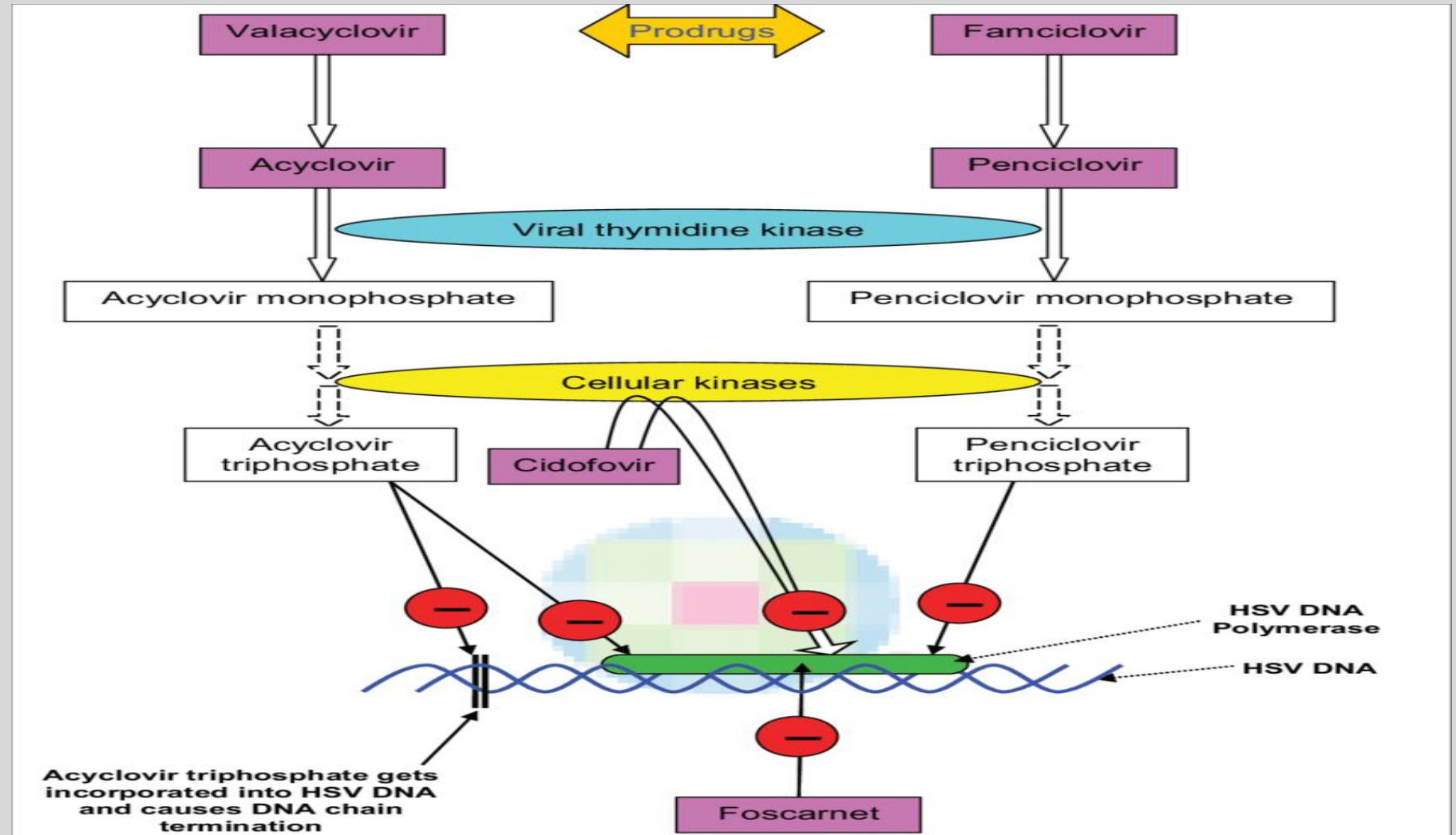
**Up to 10% (and even 30-40% in some studies) in
hematopoietic cell transplant (HCT) recipients**

Risk factors

| Host factors | Viral factors | Antiviral therapy |
|---|---------------------------|-------------------------------------|
| Haploidentical, allogeneic, or cord blood HCT | Recurrent infections | Nucleoside analogs exposure |
| HCT for Relapsed hematologic malignancies | Ongoing viral replication | Prolonged antiviral treatment |
| Hematologic malignancies | HSV-2 | Inadequate / intermittent treatment |
| Graft versus host disease | | |
| SOT (heart and lung) | | |
| Myelofibrosis | | |
| HIV/AIDS | | |
| Congenital immunodeficiency syndromes | | |
| Anti-TNF therapy | | |
| Keratitis | | |

Resistance Mechanisms

- Virus-encoded thymidine kinase (TK) (*UL23* gene)
- Viral DNA polymerase (*UL30* gene)

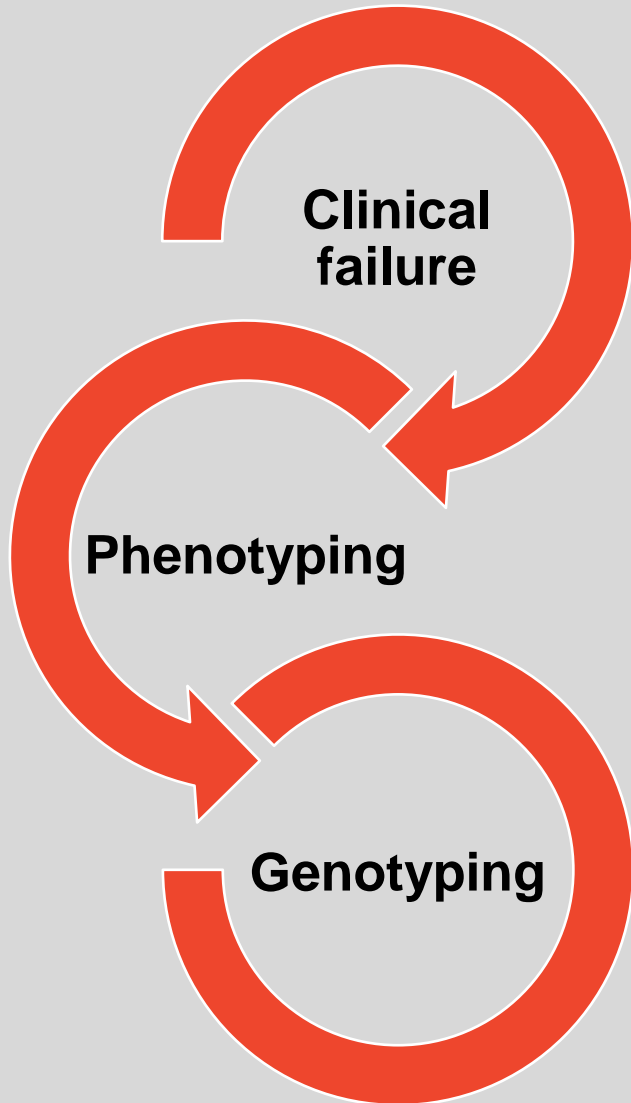


Clinical Characteristics and Outcomes

- Mostly **mucocutaneous disease**
 - **Prolonged, recurrent** and **extensive** lesions
 - **Abnormal** lesion appearance - ulcerative, hypertrophic, pseudotumor-like lesions
 - **Dissemination** to invasive disease (CNS, lung, liver) is **rare**
- In HCT recipients → **prolonged** anti-viral therapy, **recurrent** infections, **renal failure, increased risk of hospitalization**
- **Toxic** alternative treatment options (Foscarnet, Cidofovir)

Tandon S et al. Recalcitrant hypertrophic herpes genitalis in HIV-infected patient successfully treated with topical imiquimod. *Dermatol Ther*. 2017 May;30(3). doi: 10.1111/dth.12479. Anton-Vazquez V et al. Challenges of aciclovir-resistant HSV infection in allogeneic bone marrow transplant recipients. *J Clin Virol*. 2020 Jul;128:104421. doi: 10.1016/j.jcv.2020.104421. Ariza-Heredia EJ et al. Delay of alternative antiviral therapy and poor outcomes of acyclovir-resistant herpes simplex virus infections in recipients of allogeneic stem cell transplant - a retrospective study. *Transpl Int*. 2018 Jun;31(6):639-648. doi: 10.1111/tri.13142. Patel D et al. Predictors and outcomes of acyclovir-resistant herpes simplex virus infection among hematopoietic cell transplant recipients: case-case-control investigation. *Clin Transplant*. 2014 Jan;28(1):1-5. doi: 10.1111/ctr.12227.

Refractory / resistance HSV infection diagnosis



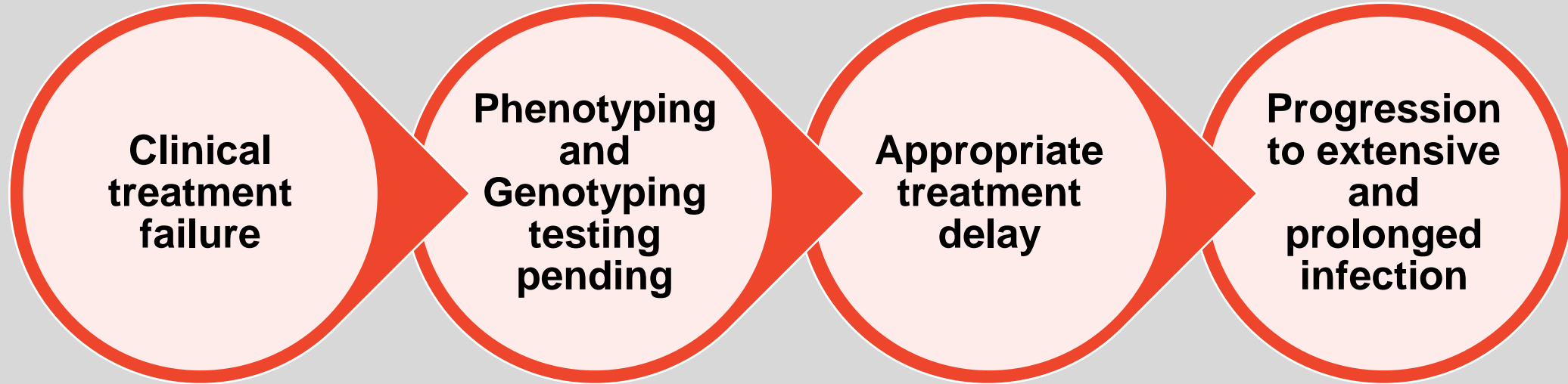
Phenotyping

- **Plaque reduction assay**
- The concentration of drug that reduces the plaque number by 50% (**IC50**)
- **Slow**
- **Subjective**

Genotyping

- Detection of specific mutations in UL23, UL30
- Sanger sequencing
- Next generation sequencing
- **Polymorphism!**

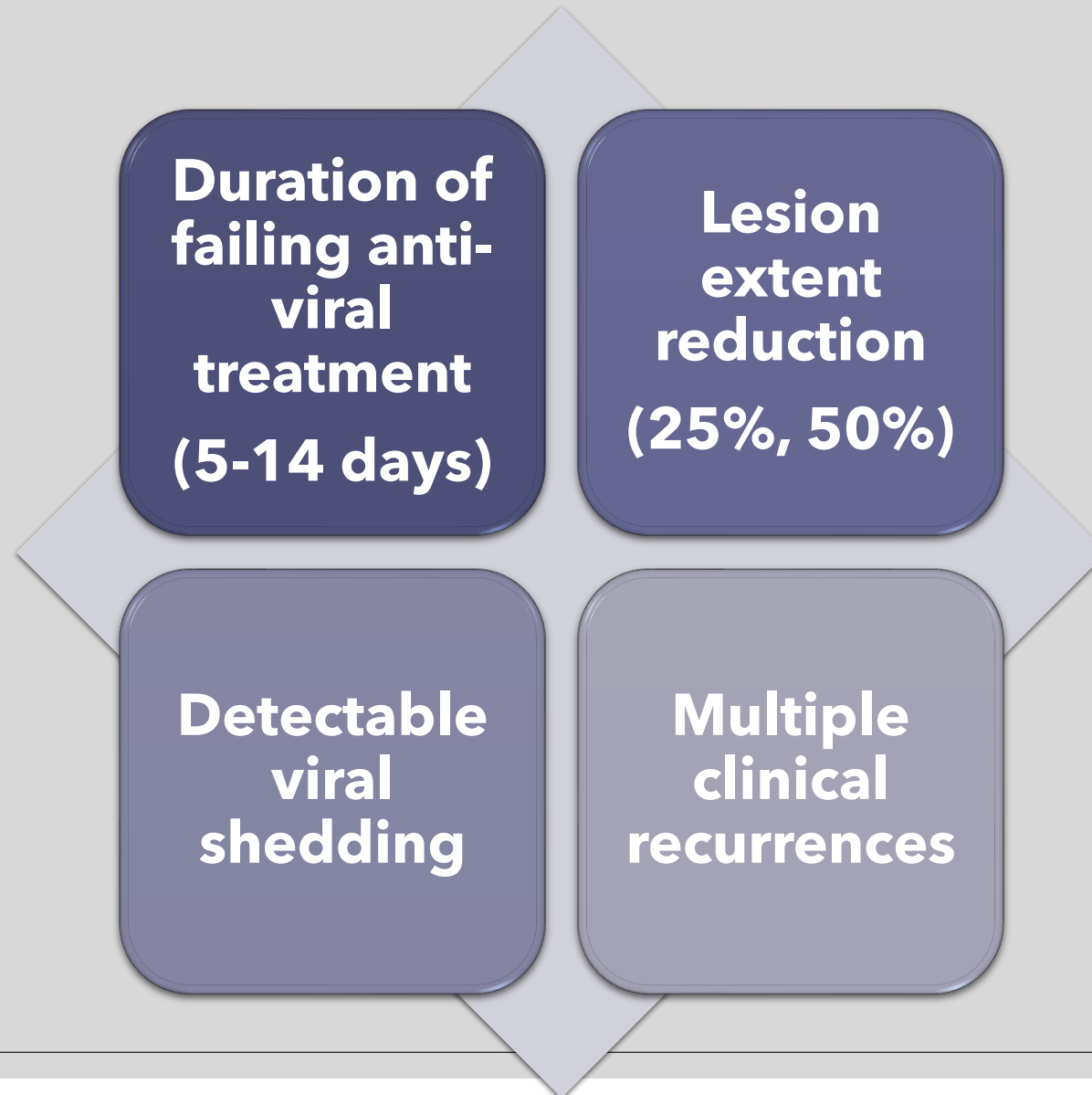
Diagnostic Challenges



Systematic review of resistant / refractory HSV infections in immunocompromised hosts

- PubMed and Embase databases
- “Herpes simplex virus or HSV”, “Resistan*”, “Refractory” and “Immunocompromised” “Immunosuppress*”, “Immunodeficien*”, excluding reviews and animal studies
- 487 titles were screened
- 196 papers reviewed
- Only 4 RCT’s from the 1990’
- Current phase III pritelivir (AiCuris) RCT definitions

Clinical failure definition components



Pritelivir protocol definitions:

- **ACV-R mucocutaneous HSV episodes:** Clinical failure or positive genotypic/phenotypic ACV resistance testing for current lesion
- **Clinical failure definition:** No improvement after oral or IV doses for at **least 7 days** at doses equivalent to or greater than the local agency approved **high doses** of acyclovir, valacyclovir or famciclovir

Time out



How would we define
refractory HSV infection clinically?

Suggested definitions for Refractory Mucocutaneous HSV infection

- **Failure of the mucocutaneous lesions to improve** (at least 25% or more? Pain relief?) OR development of new lesions after **7 days** of an **appropriate route and dosage** of anti-viral therapy

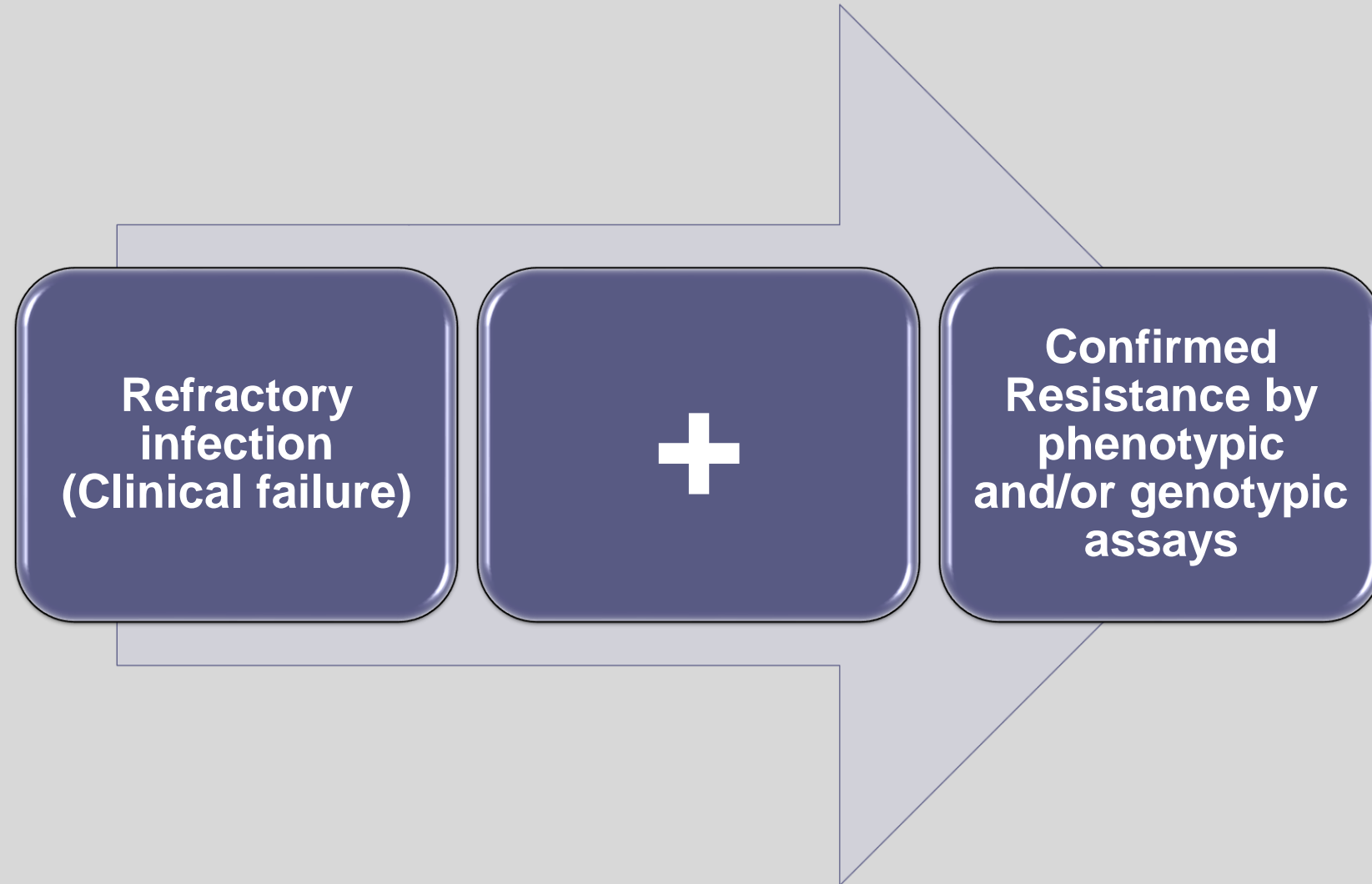
OR

- **Breakthrough** mucocutaneous infection on current therapy excluding prophylaxis or suppressive anti-viral therapy

Suggested definition for Recurrent HSV infection

- **New** HSV-related infection (mucocutaneous lesion or other) that emerges at **least 2? 4? weeks** after resolution of a previous HSV-related infection episode

Suggested definition for Drug Resistant HSV infection



Take home messages

- **Refractory/resistant HSV infections are not uncommon** in immunocompromised population
- **Consensus definitions** for refractory and resistant HSV infection **are needed** for clinical trials and research use
- **Genotyping methods** are improving and allowing **rapid** detection of mutations
- **New treatment options** are needed