Microbial Immune Evasion and Persistence

Lecturer: William Halford
Overview

1. Introduction to persistent infections

2. Strategies that promote microbial persistence

3. Alphaherpesviruses: a case study in persistence
Overview

1. Introduction to persistent infections
   - microbial growth in vivo
Microbial replication in the lab

- **Log phase bacterial growth**
- Lag phase
- Log, or exponential growth, phase
- Stationary phase
- Death, or logarithmic decline, phase

Time (hours)
Microbial growth *in vivo*

![Graph showing microbial growth over time](image)
Microbial growth *in vivo*

Microbial growth:
- Incubation period
- Plateau

Expression:
- Rate of microbe replication = Rate of immune clearance

Graph:
- Microbe burden/load over time (days):
  - Incubation period
  - Plateau

0 7 14 21

Time (days)
Microbial growth *in vivo*

A graph showing the growth of microbe burden/load over time (days) with three distinct periods:
- **Incubation period**
- **Plateau**
- **Convalescent period**

The graph indicates that the rate of microbe replication is much less than the rate of immune clearance.
Acute infection

- Incubation period
- Plateau
- Convalescent period
- Resolution

Microbe burden/load vs. time (days)

0 7 14 21
Persistent infection

- Incubation period
- Plateau
- Convalescent period
- Resolution

Microbe burden reduced, but not cleared
Overview

1. Introduction to persistent infections
   - microbial growth *in vivo*
   - Why do some infections persist?
Microbial infections exist in an equilibrium *in vivo*.

Microbe production *in vivo* = rate of microbe replication – rate of microbe clearance (immune killing)
When equilibrium tips in favor of microbe.....
.....acute infection progresses.
When equilibrium tips in favor of host response.....
....acute infection resolves.
When microbial replication and host response generate equal and opposing forces...**persistent infection**.

- **microbe**  
  - host response

- microbe persists while  
  host response limits spread
Equilibrium concept = key to understanding persistent infections
Equilibrium concept = key to understanding persistent infections

- Microbiome / load
- Immune control
- Host response
- Replication
- HSV
- CD3
- Neuron
- T cells
Overview

1. Introduction to persistent infections
   - microbial growth *in vivo*
   - why do some infections persist?
   - chronic versus latent infections
Chronic infection: high level of replication (high burden) during clinically “latent” phase.
**Latent infection**: replication not detectable (low burden) during clinically “latent” phase

![Graph showing the timeline of infection](image)

- **Acute phase**: High microbial burden
- **Clinically “latent” phase**: Low microbial burden, not detectable
- **Immune control**: Host response manages the infection

**Graph Notes**:
- **Time (months)**: 0 to 6
- **Microbe burden/load**: Measured along the vertical axis

The diagram illustrates the transition from the acute phase to the clinically “latent” phase, highlighting the role of the host response in controlling microbial replication.
Recurrent infection: microbial replication resumes → new disease

- acute phase
- "latent"
- recurrent disease
- "latent"

- replication
- immune control
- host response

Time (months)

0  2  4  6
Overview

1. Introduction to persistent infections

2. Strategies that promote microbial persistence
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION
- Intracellular invasion

*Plasmodium falciparum*
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION
- Intracellular invasion

Plasmodium falciparum

Mycobacterium tuberculosis

Salmonella typhimurium
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION

- Intracellular invasion
- Downregulation of antigen synthesis (latency)

Herpesviruses

Mycobacterium tuberculosis
Antigenic shutdown (latency)

**Latency**: an indefinite period of reduced, or no, protein synthesis that allows a microbe to become antigenically “invisible.”

No antigen → no detection by immune system

- **Herpesviruses**
- **Mycobacterium tuberculosis**

**Diagrams**:
- Immune control
- Microbe → Host response
- Replication
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION
- Intracellular invasion
- Downregulation of antigen synthesis (latency)
- Polysaccharide cloaking device (capsule)
  - Deposition of C3b and antibody inefficient

Klebsiella pneumoniae

immune control

microbe  host response

replication
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION

Strategy 2. Use of DNA as genetic material
  - Chemically stable over time.
  - May persist in absence of active replication.
Viral persistence: DNA vs RNA viruses

DNA viruses that persist for more than 6 months:
- all herpesviruses (8 human viruses)
- all retroviruses (proviral form)
- hepatitis B virus
- adenovirus
- papillomavirus
- molluscum contagiosum virus (poxvirus)

RNA viruses that persist:
- hepatitis C virus (has to replicate to be maintained)
1st phase of Retrovirus life cycle (hours)
2nd phase of Retrovirus life cycle (days - years)
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION
Strategy 2. Use of DNA as genetic material

Strategy 3. Change major antigens to avoid RECOGNITION
   A. Antigenic drift of HIV (within carrier)
   B. Antigenic-phase variation (within carrier)
Flagella are a major antigen in many bacteria
Salmonella encode >1 flagella: antigenic phase variation
Salmonella encode >1 flagella: antigenic phase variation

DNA inversion in 0.01% of bacteria
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION
Strategy 2. Use of DNA as genetic material

Strategy 3. Change major antigens to avoid RECOGNITION
   A. Antigenic drift of HIV (within carrier)
   B. Antigenic-phase variation (within carrier)
      • *Salmonella species*
      • *Borrelia species* (e.g., Lyme disease)
      • *Trypanosomases* (e.g., African sleeping sickness)
Antigenic phase variation

Trypanosomes
Antigenic phase variation

![Graph showing antigenic phase variation and expression sites of Trypanosomes]
Antigenic phase variation

Trypanosomes

Antibodies to variant 2

Antibodies to variant 1

(b)

Expression site

Dissociation and translocation to expression site

Expression site

Million of trypanosomes per million of blood

Approximate time after tsetse fly bite, weeks

5'-VSG1- VSG2- VSG4- VSG3- VSG4- VSG1- 3'

5'-VSG1- VSG2- VSG4- VSG3- VSG4- VSG1- 3'
Antigenic phase variation

Trypanosomes

(b) [Diagram showing duplication and translocation to expression site]
Antigenic phase variation

![Antigenic phase variation diagram](image)
Antigenic phase variation: antigenic shift within a single host

Trypanosomes
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION
Strategy 2. Use DNA as genetic material
Strategy 3. Change major antigens to avoid RECOGNITION
Strategy 4. Colonize sites difficult to ATTACK

Echinococcus tapeworm

Mycobacterium tuberculosis

hydatid cysts
granuloma
Microbes that persist evade immune clearance

Strategy 1. Hide major antigens to avoid RECOGNITION
Strategy 2. Use of DNA as genetic material
Strategy 3. Change major antigens to avoid RECOGNITION
Strategy 4. Colonize sites difficult to ATTACK

Strategy 5. Active obstruction of immune effector mechanisms
- *Staph aureus* protein A → binds IgG’s Fc region
- renders bacteria opsonization-resistant
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3. Alphaherpesviruses: a case study in persistence
   A. Alpha-herpesviruses
   B. Immunity to viruses
   C. HSV-encoded countermeasures
   D. The “paradox” of recurrent herpes
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   A. Alpha-herpesviruses
      • The players
Herpesviruses

Marek's Disease Virus
Pseudorabiesvirus
macropodid herpesvirus 1
crocodylid herpesvirus 1
ostreid herpesvirus 1
All herpesviruses.....

- encode conserved set of 42 genes that synthesize and package viral dsDNA into virions
- Establish life-long infections in host
- Remain latent for long periods
- Reactivate episodically, make new virions $\rightarrow$ transmission
Tropism.

- Broadly, the herpesviruses can be divided based on their use of neurons or leukocytes as their permanent homes.

In humans......

- **Neurotropic** (α-herpesviruses)
  - Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2)
  - Varicella-Zoster Virus (VZV)

- **Blood-borne** (β- and γ-herpesviruses)
  - Cytomegalovirus, HHV-6, HHV-7 >> monocytes (β-herpesviruses)
  - Epstein-Barr Virus, HHV-8 >> lymphocytes (γ-herpesviruses)
Herpes simplex virus type 1

Primary infection
virus spreads to trigeminal
ganglion neurons
Herpes simplex virus type 1

Recurrent infection
months to years later,
virus reactivates
and spreads back to lip
Human α-herpesviruses

- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
Herpes simplex virus type 2

Primary infection
virus spreads to sacral
ganglia neurons
Herpes simplex virus type 2

Recurrent infection

months to years later, virus reactivates and returns to genitalia
Human \(\alpha\)-herpesviruses

- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Varicella-zoster virus (VZV)
Primary infection: varicella
virus spreads by viremia and nerves to
trigeminal ganglia and all spinal ganglia
Varicella-zoster virus

VZV BECOMES LATENT IN THE NERVE GANGLIA

CHICKEN POX

REAKTIVATES YEARS LATER

SHINGLES
Varicella-zoster virus

Recurrent infection: **zoster**

virus reactivates in 1 ganglion and
disease limited to 1 dermatome
Varicella-zoster virus

Recurrent infection: **zoster**

virus reactivates in 1 ganglion and
disease limited to 1 dermatome
Varicella-zoster virus

Recurrent infection: *zoster*

virus reactivates in 1 ganglion and
disease limited to 1 dermatome
Alphaherpesvirus latency: an equilibrium

virus ↔ host response

HSV-1 latency: viral genome

CD8+ T cells

IFN-γ

HSV+ neuron

CD3+ T cells

HSV-1 replication:

viral activators

ICP0, ICP34.5

viral genome

host immunity
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   A. Alpha-herpesviruses
      ● The players
      ● Basic biology of HSV
Herpes simplex virus 1

Large DNA virus that is:

• 152,000 bp.
• contains ~75 genes.
• too large to meaningfully discuss gene by gene……..
HSV gene functions.

5 IE proteins:
modify the cell’s transcriptional machinery and thus create environment that allows E gene expression

25 E proteins:
- 5 nucleotide synthesis enzymes (thymidine kinase)
- 7 DNA replication proteins (HSV DNA polymerase)

45 L proteins:
- 5 capsid proteins (VP5)
- 15 tegument proteins (VP16)
- 11 glycoproteins (gD)
- 6 involved in nucleocapsid assembly (protease, endonuclease)
Steps in HSV replication

1. Adsorption and Entry (gB and gD)

Figure 41.3. Productive infection of a cell by a herpesvirus. The virions are not drawn to scale. In reality they are much smaller in proportion to the cell.
Steps in HSV replication
2. Transport to nucleus

Figure 41.3. Productive infection of a cell by a herpesvirus. The virions are not drawn to scale. In reality they are much smaller in proportion to the cell.
Steps in HSV replication
3. Viral IE and E gene expression

Figure 41.3. Productive infection of a cell by a herpesvirus. The virions are not drawn to scale. In reality they are much smaller in proportion to the cell.
Steps in HSV replication
4. Viral DNA synthesis

VP16 $\rightarrow$ IE mRNAs $\rightarrow$ IE proteins

DNA replication

E mRNAs $\rightarrow$ E proteins

Cell surface receptors

Cell nucleus

Viral assembly

Figure 41.3. Productive infection of a cell by a herpesvirus. The virions are not drawn to scale. In reality they are much smaller in proportion to the cell.
Steps in HSV replication
5. virion synthesis / egress

L mRNAs → L proteins (45)

DNA replication

Synthesis of structural and nonstructural protein

Cell surface receptors

Cell nucleus

Viral assembly

The virions are not drawn to scale. In reality, they are much smaller in proportion to the cell.
A bit more to scale......

**Figure 41.3.** Productive infection of a cell by a herpesvirus. The virions are not drawn to scale. In reality they are much smaller in proportion to the cell.
HSV-2 spread over 4 cycles of replication

Green HSV-2 (8 h after infection)
HSV-2 spread over 4 cycles of replication

Green HSV-2 (8 h after infection)

Green HSV-2 (56 h after infection)
Overview

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   A. Alpha-herpesviruses
      - The players
      - Basic biology of HSV
      - HSV spread *in vivo*
        - animal models
Green HSV in mice ± immune system

1. Inoculate mice with green HSV virus in eyes
2. photograph mouse eyes & faces over time

(HSV-GFP)
Balb/c mice + no treatment

(HSV-GFP)
Balb/c mice + $\gamma$-irradiation

(HSV-GFP)
Balb/c mice + cyclophosphamide
GFP$^+$ herpes simplex virus in a mouse eye

Day 1
GFP⁺ herpes simplex virus in mice

Day 3

normal  𝛾-irradiated  cyclophosphamide
GFP\textsuperscript{+} herpes simplex virus in mice

Day 4

normal  \hspace{5mm} \gamma\text{-irradiated}  \hspace{5mm} \text{cyclophosphamide}
GFP⁺ herpes simplex virus in mice

Day 5

normal  γ-irradiated  cyclophosphamide
GFP+ herpes simplex virus in mice

Day 6

normal  \( \gamma \)-irradiated  cyclophosphamide
GFP⁺ herpes simplex virus in mice

Day 7

normal  γ-irradiated  cyclophosphamide
GFP$^+$ herpes simplex virus in mice

Day 9

normal  $\gamma$-irradiated  cyclophosphamide
Why this pattern of HSV spread in animals?

- nerve fibers = primary conduit of viral spread
- virus → host immune response

normal  γ-irradiated  cyclophosphamide
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      • The players
      • Basic biology of HSV
      • HSV spread *in vivo*
        - animal models
        - in humans
Spread of HSV-1 infection
Day 1

1. Primary Infection
Spread of HSV-1 infection
Day 2
Spread of HSV-1 infection
Day 3
Spread of HSV-1 infection
Day 5
Slowing of HSV-1 spread
Day 7
HSV-1 infection is latent
(Day 14 - decades later)

2. Latent infection.
3. Reactivation of latent HSV genome.

Common triggers:
- sunburn
- fever
- “exam stress”

Virus spread to new host.
Other presentations of recurrent herpes.
Clinical presentations of recurrent herpes.
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   A. Alpha-herpesviruses
   B. Immunity to viruses
Host immunity: hurdles to viral disease

- Epithelium / innate barriers
- Interferon / innate immunity
- B cells / antibody
- CD8+ T cells
Hurdle 1: The Interferon System
Resistant to viral infection

IFN-α/β

Upregulation of:
- MHC class I
- PKR

Host Interferon Response

Resistant to viral infection
Effect of interferon on viral replication?

- Cells + no interferon
- Cells + interferon-α
Effect of interferon on viral replication

Each red dot = 1 viral plaque

cells + no interferon

cells + interferon-α
**Interferons: an innate defense against viral spread**

**Interferon**: a virus-induced warning system that renders cells adjacent to a site of virus replication resistant (non-permissive) before infectious virions reach these cells.
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   B. Immunity to viruses
      • interferon-induced antiviral state
      • antibodies to viruses
Next hurdle: neutralizing, virus-specific antibodies
Neutralizing antibodies
(competitive antagonists that bind to virion receptors)

Viruses: mechanism of action.

Step 1  Step 2  Step 3

Virion binds cell
Virion enters cell
Virus released; infection starts

Neutralizing antibodies block Step 1.

Antibody blocks virion receptors
**Virus-specific antibodies**: prevent viremia, serve a pro-inflammatory role in virus-infected tissues (recruit WBCs)
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   A. Alpha-herpesviruses
   B. Immunity to viruses
      - interferon-induced antiviral state
      - antibodies to viruses
      - CD8+ T-cells
CD8⁺ T cells RECOGNIZE viral peptides + MHC I

- MHC class I is essential for CD8⁺ T cells to RECOGNIZE virus-infected cells.
Virus-specific CD8$^+$ T cells kill virus-infected cells
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   C. HSV-encoded countermeasures
Host defense against viruses: **interferons** and T cells
Effect of interferon on viral replication

cells + no interferon

cells + interferon
Viruses encode countermeasures to host interferons

- inhibitors of PKR
  - EBER (EBV)
  - K3L (vaccinia)
  - VAI (adenovirus)
  - TAR and tat (HIV)
  - US11 (HSV)
Viral countermeasures to host interferons

- Inhibitors of PKR
- Soluble IFN-α / β receptor
  - B18R (vaccinia)

Upregulation of:
- MHC class I
- PKR

Resistant to viral infection
Viral countermeasures to host interferons

- inhibitors of PKR
- soluble IFN-α / β receptor
- reverses effects of IFNs
  - ICP0, ICP34.5 (HSV)
  - vIRF K9 (HHV-8)
  - E1a (adenovirus)
Poxviruses take this concept one step further....
Poxviruses hijack the entire host cytokine response

**DECOY RECEPTORS**
- v TNF receptor
- v IL-1β receptor
- v IFN-γ receptor
- v IFN-α/β receptor

**VIRAL CYTOKINES**
- v IL-8
- v IL-10
- v IL-17
- v IL-6

**CYTOKINE BINDING PROTEINS**
- vIL-2 binding protein
- vIL-18 binding protein
- vIFN-γ binding protein

Molluscum contagiosum

smallpox
Host defense against viruses: interferons and T cells

Ag presentation and CTL @ http://www.hhmi.org/biointeractive/disease/animations.html#ecoli
CD8$^+$ T cells RECOGNIZE viral peptides within MHC class I

- MHC class I is essential for CD8$^+$ T cells to RECOGNIZE virus-infected cells.

![Diagram of viral peptide presentation by MHC class I](image)
Some viruses prevent MHC class I from reaching cell surface. (block RECOGNITION).

Evasion of CD8⁺ T cells

(no MHC class I  →  no RECOGNITION)
MHC class I immune evasion slides
Viral countermeasures to MHC class I pathway

- **Block TAP (antigen loading)**
  - ICP47 (HSV)
  - US6 (CMV)
- **Retain MHC I in ER**
  - E3 (adenovirus)
  - US3 (CMV)
- **Target MHC I for degradation**
  - US2 and US11 (CMV)
  - Vpu (HIV)
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   B. Immunity to viruses
   C. HSV-encoded countermeasures
   D. The “paradox” of recurrent herpes
Host “immunity” and recurrent viral disease

- Paradox: people who experience recurrent herpes often have the highest level of “immunity” to HSV.
  - e.g., highest levels of HSV-specific IgG antibody
Host “immunity” and recurrent viral disease

- Paradox: people with recurrent herpes have “immunity” to HSV.
  - e.g. high levels of HSV-specific IgG antibody

- Consider the mechanisms that confer antiviral immunity.
  - interferon-induced antiviral state
1. Interferon-induced block

Observation

- HSV infection activates cellular PKR
- PKR activity shuts off viral protein synthesis
- HSV IE genes
  - E genes
  - L genes
- P-eIF-2α
- PKR activated

no new virions = no viral spread
Observation

HSV ICP34.5 = interferon antagonist

HSV IE genes

E genes

L genes

no new virions = no viral spread
Observation

HSV ICP34.5 removes block

ICP34.5 restores viral protein synthesis

HSV IE genes

E genes

L genes

HSV ICP34.5 removes block

ICP34.5 restores viral protein synthesis

Protein Phosphatase 1

eIF-2α

P

Phosphorylated
Host “immunity” and recurrent viral disease

- Paradox: people with recurrent herpes have “immunity” to HSV.
  - e.g. high levels of HSV-specific IgG antibody

- Consider the mechanisms that confer antiviral immunity.
  - ICP34.5 → interferon-induced antiviral state
Host “immunity” and recurrent viral disease

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- Consider the mechanisms that confer antiviral immunity.
  - ICP34.5 → interferon-induced antiviral state
  - Antibodies
Antibodies

- Soluble mediators of RECOGNITION that tag proteins or cells expressing foreign proteins for destruction / clearance.
HSV-1 glycoprotein E-glycoprotein I: prevent immune system from RECOGNIZING antibody tags bound to HSV-1 infected cells.
Host “immunity” and recurrent viral disease

- Paradox: people with recurrent herpes have “immunity” to HSV.
  - e.g. high levels of HSV-specific IgG antibody

- Consider the mechanisms that confer antiviral immunity.
  - ICP34.5 $\rightarrow$ IFN-α/β-induced antiviral state
  - glycoprotein E-I dimer $\rightarrow$ IgG antibody
Host “immunity” and recurrent viral disease

- Paradox: people with recurrent herpes have “immunity” to HSV.
  - e.g. high levels of HSV-specific IgG antibody

- Consider the mechanisms that confer antiviral immunity.
  - ICP0 → IFN-α/β-induced antiviral state
  - glycoprotein E-I dimer → IgG antibody
  - complement cascade
Host “immunity” and recurrent viral disease

- Paradox: people with recurrent herpes have “immunity” to HSV.
  - e.g. high levels of HSV-specific IgG antibody

- Consider the mechanisms that confer antiviral immunity.
  - ICP34.5 → IFN-α/β-induced antiviral state
  - glycoprotein E-I dimer → IgG antibody
  - glycoprotein C → binds C3b split product
Host “immunity” and recurrent viral disease

- Paradox: people with recurrent herpes have “immunity” to HSV.
  - e.g. high levels of HSV-specific IgG antibody

- Consider the mechanisms that confer antiviral immunity.
  - ICP0 and ICP34.5 $\rightarrow$ IFN-\(\alpha/\beta\)-induced antiviral state
  - glycoprotein E-I dimer $\rightarrow$ binds IgG antibody
  - glycoprotein C $\rightarrow$ binds C3b split product
  - CD8$^+$ T cells
ICP47 binds TAP no MHC class I
Host “immunity” and recurrent viral disease

- Paradox: people with recurrent herpes have “immunity” to HSV.
  - e.g. high levels of HSV-specific IgG antibody

- Recurrent herpes is not a paradox, when you consider that HSV actively obstructs all three arms of antiviral immunity.
  - ICP34.5: innate immunity
  - gC + gE-gI: humoral immunity
  - ICP47: cell-mediated immunity
3. Reactivation of latent virus
4. Disease. Spread of virus to new host.

HSV comes out.... over and over again.
Epidemiology: 
*seroprevalence versus viral disease*

- **Seroprevalence in United States**
  - herpes simplex virus 1 (HSV-1): ~200 million (66%)
  - herpes simplex virus 2 (HSV-2): ~50 million (16%)

- **Severity of disease**

<table>
<thead>
<tr>
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<th>HSV-1†</th>
<th>HSV-2†</th>
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<tbody>
<tr>
<td>unaware of infection:</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>recurrent herpes infections ( &gt;4/ yr):</td>
<td>1%</td>
<td>2% (~3 million in U.S.)</td>
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Herpesvirus persistence: key features

1. **Latent state = stable reservoir of virus-infected cells.**
   - ability to go into hiding explains success of human herpesviruses
     - most of us are infected with 4 of the 8; HSV-1, VZV, CMV, and EBV

2. **Immune evasion = promotes transmission after reactivation.**
   - reactivation = low-level / single cell herpesviral replication events
   - immune evasion proteins delay immune RECOGNITION long enough that virions may be shed and transmitted to next person
Take-home message

- Microbes that persist in humans typically employ one or more strategies to do so:
  - intracellular invasion
  - antigenic drift
  - latency, and/or
  - immune-evasion strategies
  - antigenic phase variation
  - colonize sites difficult to ATTACK
Take-home message

- Microbes that persist in humans typically employ one or more strategies to do so:
  - Chronically
  - Episodically
  - Latent with infrequent recurrences

- Those microbes that persist establish infections that are:
  - Chronic
  - Episodic
  - Latent with infrequent recurrences
What is the difference between true love and herpes?
Herpes is forever
(because it evades the immune system)