



# ANTIRETROVIRAL DRUG RESISTANCE



# OBJECTIVES



- What is drug resistance?
- How does drug resistance happen?
- What is the link between adherence and resistance?
- What are the implications of drug resistance?



# RESISTANCE ANALOGIES



- HIV is like a colony of cockroaches. Resistance is when they keep getting sprayed but don't die.
- Resistance is similar to our past treatment of malaria. We used to treat malaria with chloroquine, but now it's not as effective.

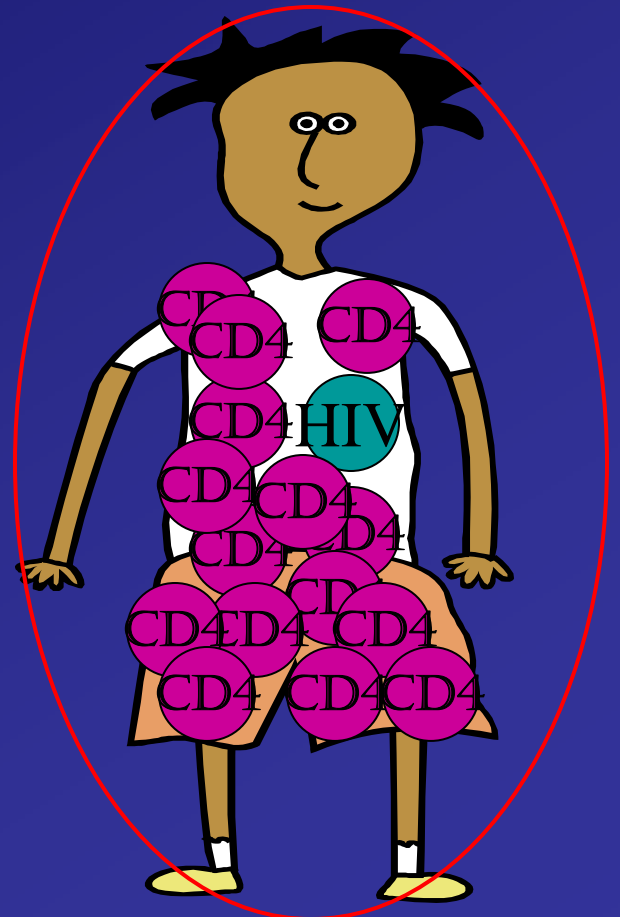
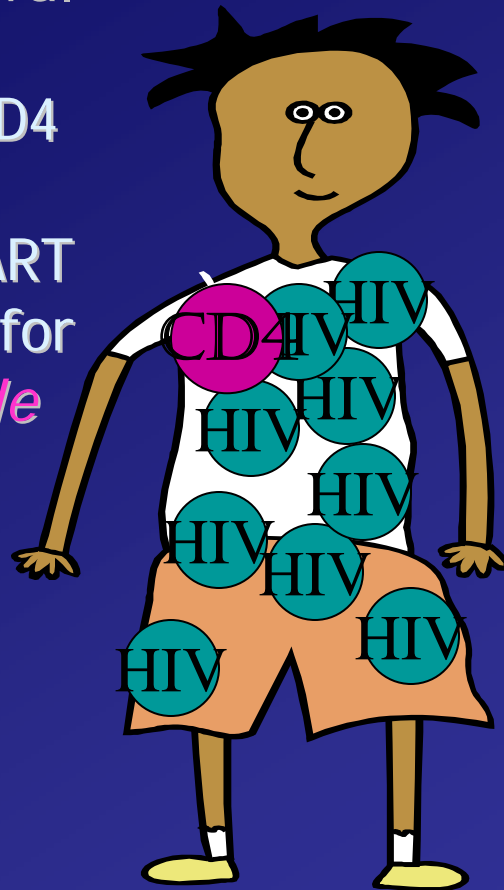


# GOALS OF HIV THERAPY



*To keep you healthy and feeling well by*

- Keeping your viral load **LOW**
- Keeping your CD4 cell count **HIGH**
- Allowing your ART regimen to work for *as long as possible*



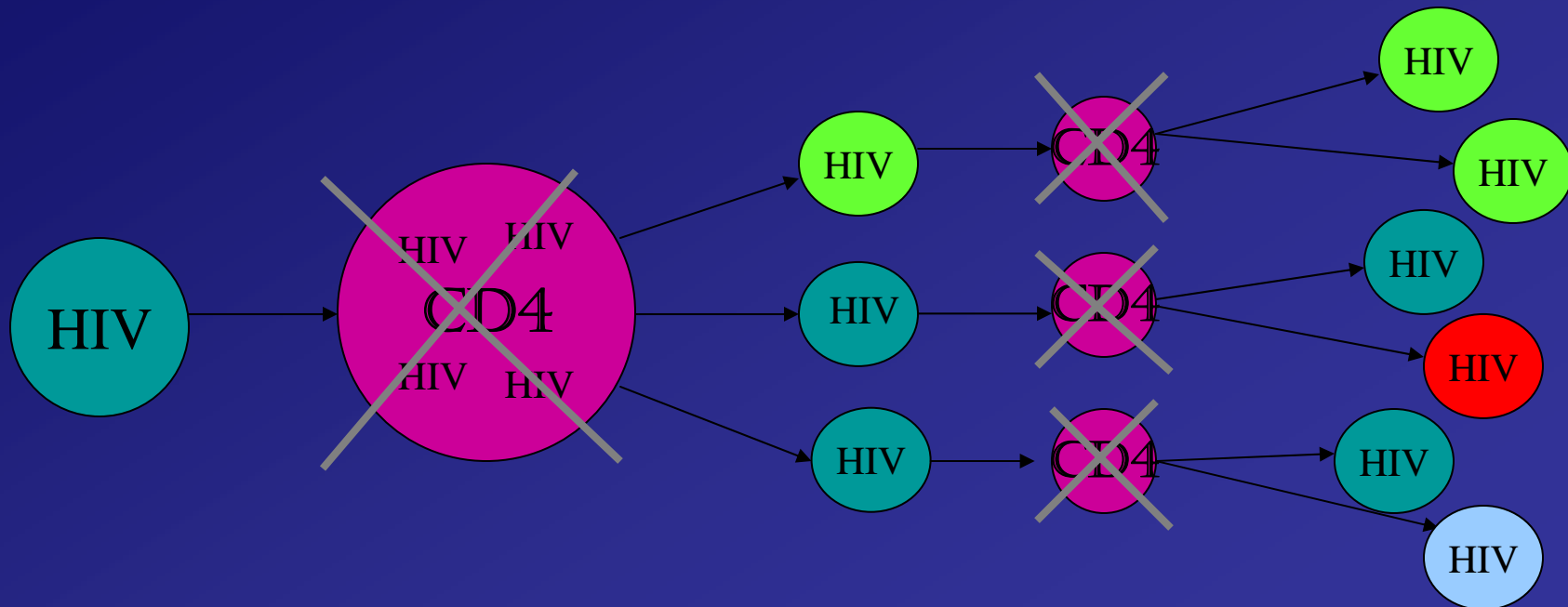


# WHAT IS DRUG RESISTANCE?



A reduction in the ability of a drug, or a combination of drugs, to block HIV replication

**HIV virus reproduces and mutates every day, continuously and consistently**





# WHAT IS DRUG RESISTANCE?



- HIV virus half-life = 30 minutes
  - $10^9$  -  $10^{10}$  viruses produced in one day

Approximately 1,000,000,000 - 10,000,000,000 virus in a day!

- Within all this new growth, ~1 mutation per viral copy occurs daily
  - Mutation rate of  $10^{-4}$  = 1 mutation for every 1,000 virus

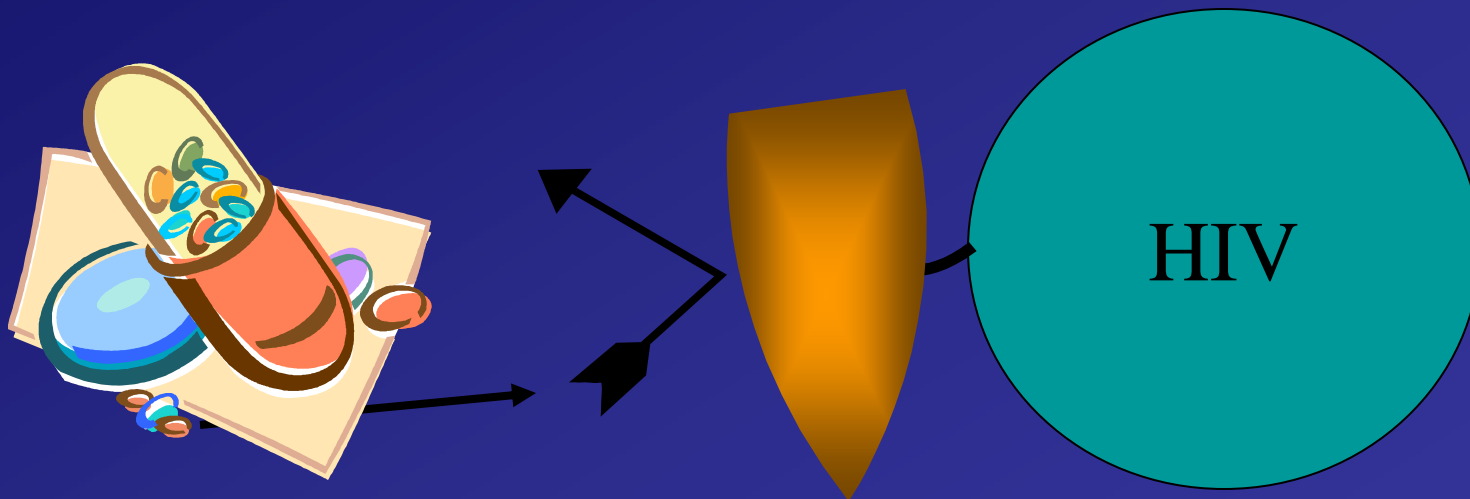
Approximately 1,000,000 - 10,000,000 mutations in a day!



# WHAT IS HIV DRUG RESISTANCE?



- Some “mutations” or changes can make your drugs stop working
- When your drugs stop working, the virus will be able to reproduce more freely—even if you still take your drugs
- Then you need to *switch* to a different ARV

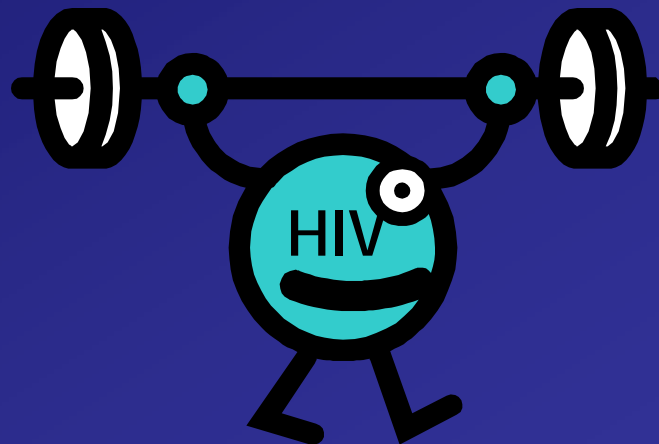




# HIV IS EITHER RESISTANT OR IT'S NOT, RIGHT?



- No. Resistance usually **develops gradually** over time.
- As resistance develops, your ARVs will not work **as well**.
- Eventually your ARVs won't work at all, and you'll have to switch to new medication.

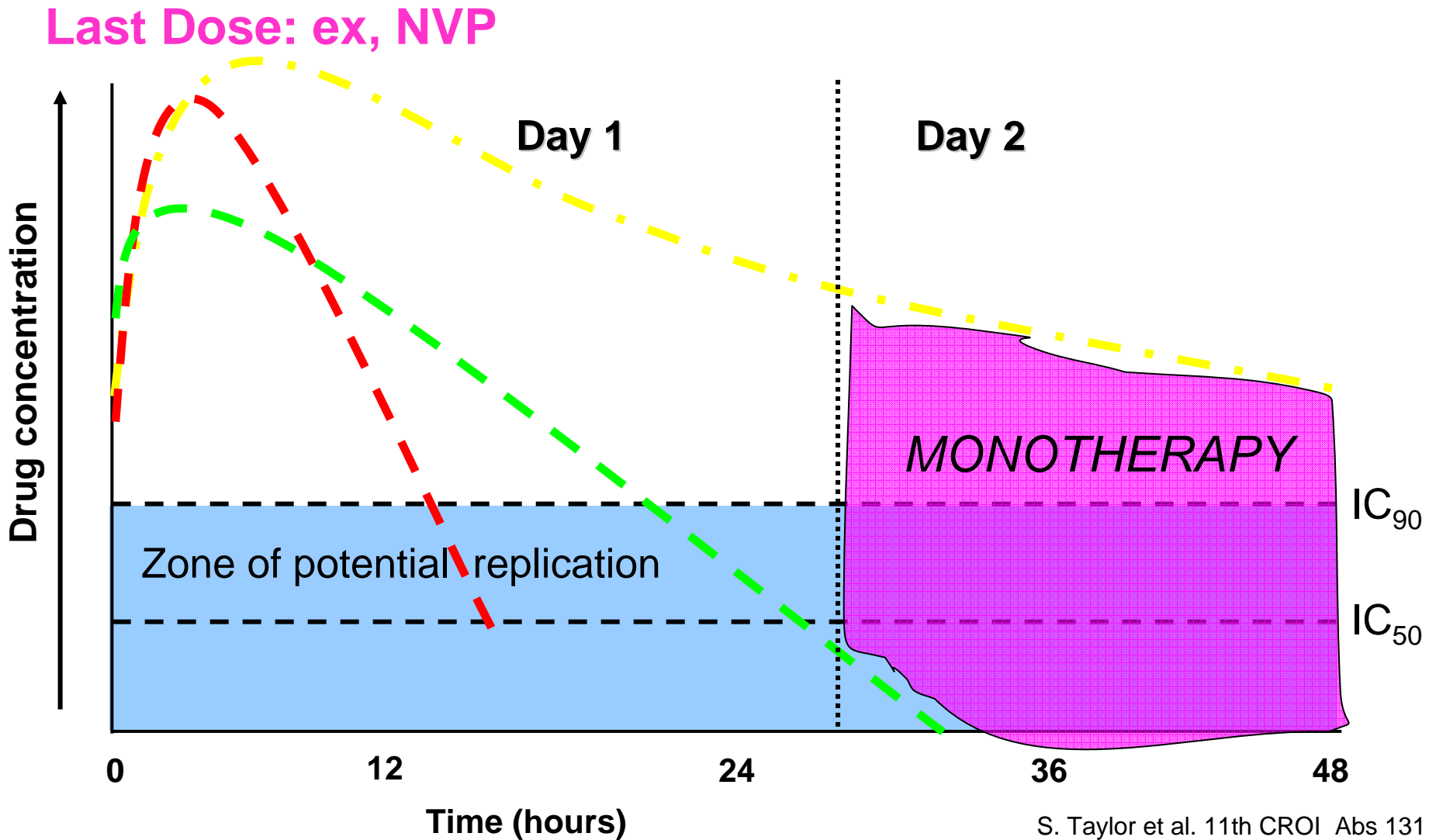


# WHAT CAUSES DRUG RESISTANCE TO DEVELOP?

Problem	Impact	Solution
Poor quality or low potency ARVs	Virus not suppressed	Ensure excellent quality meds from reputable sources
ARVs not taken properly, i.e., poor adherence	Presence of side effects, lifestyle issues not resolved, adherence not anchored	Educate, prepare, monitor patient's adherence behaviors
Drug – drug interactions	Virus not suppressed	Prepare and manage for such interactions
Individual's pharmacokinetic profile	Absorption, distribution, metabolism, removal of ARVs the body varies per person	Come in for clinic visits and monitor patient regularly

If unresolved, leads to an **increase in amount of viral load** in the body and **formation of resistant mutations**.

# Different pK Profiles in ARV Regimen May Unintentionally Lead to Resistance, “NVP Tail”





# HOW DOES RESISTANCE HAPPEN?



## ***MOST RESISTANCE IS A RESULT OF NON-ADHERENCE***

- Good adherence makes the drugs work for a long time
- Lack of adherence allows the virus to overcome the drugs
- Even missing few doses can quickly allow the virus to grow

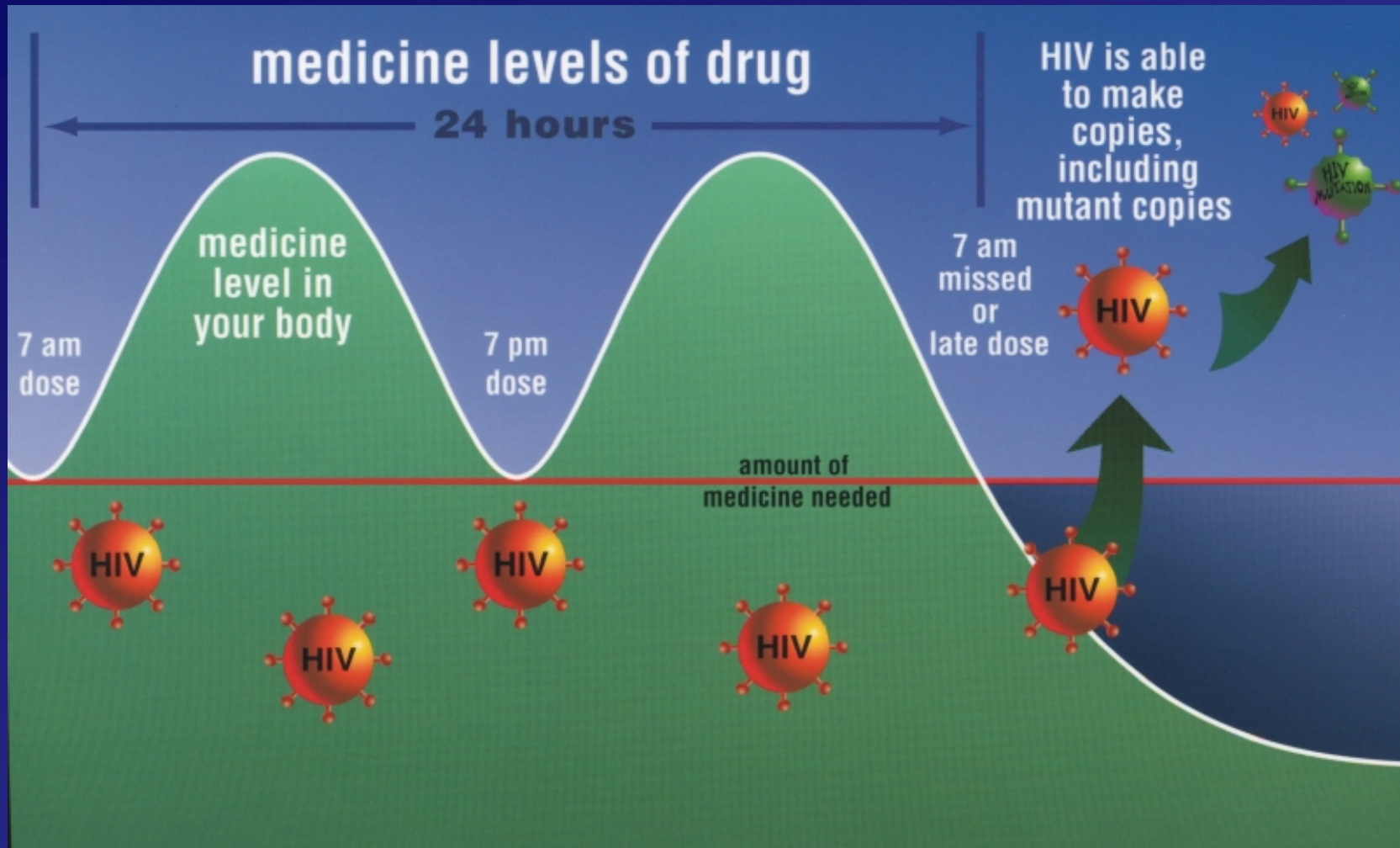




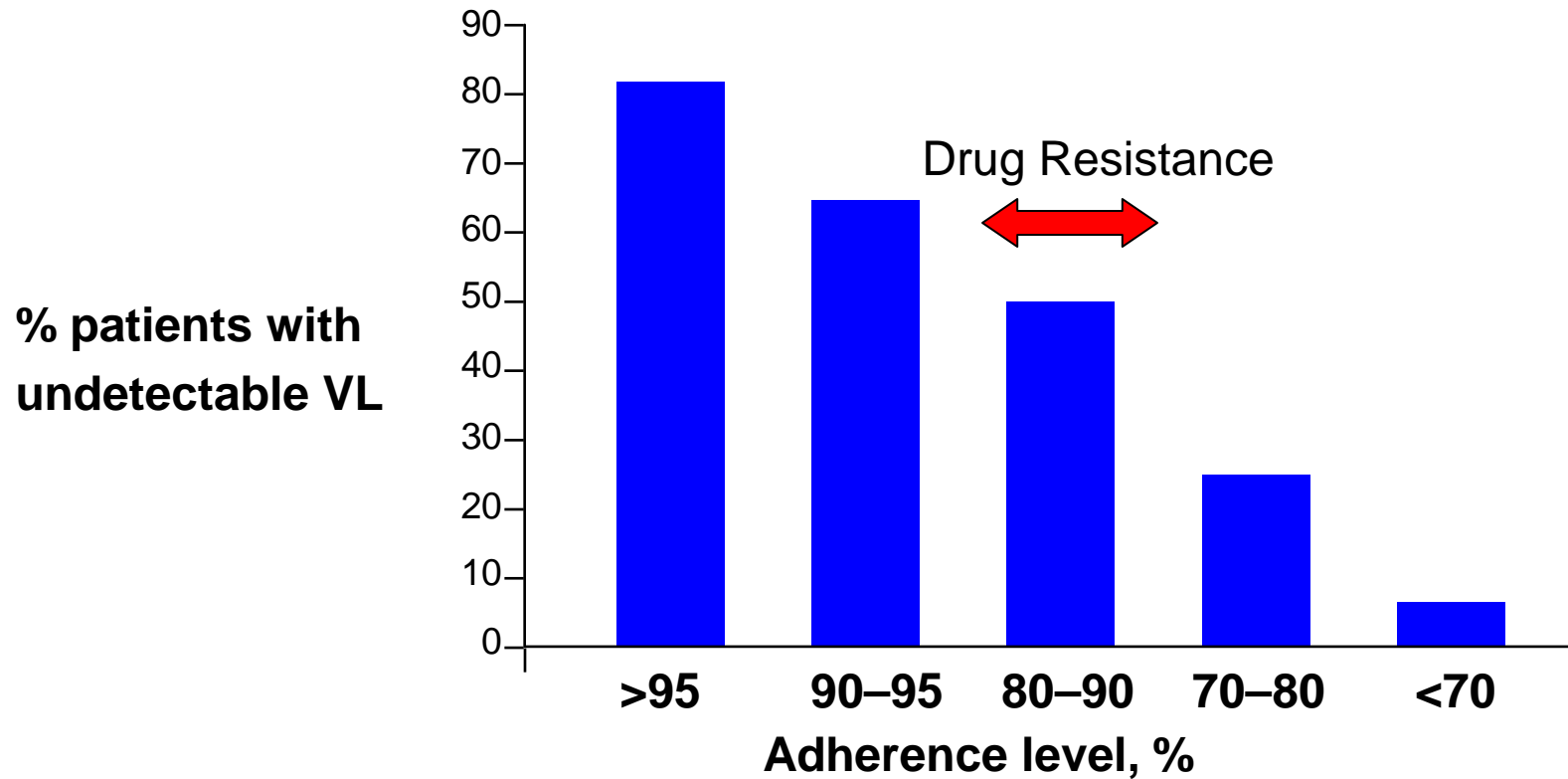
# HOW DOES RESISTANCE HAPPEN?



YOUR BODY NEEDS A CERTAIN AMOUNT OF MEDICINE TO SUPPRESS THE VIRUS



# HOW DOES RESISTANCE HAPPEN?



*Poor adherence leads to ARV ineffectiveness, faster progression to AIDS and development of resistance.*



# Link between adherence and resistance



- *Excellent adherence favorably*
  - impacts the duration of treatment response
  - minimizes need for viral load testing
- *Lack of initial or ongoing adherence results in:*
  - virologic and clinical failure
  - increased complexities and costs of care
- Even **minor decrements** in adherence can quickly reverse viral suppression
- **Maximum** drug resistance occurs in patients achieving **75-85%** adherence rates



# What is 95% adherence?



- **95% or greater adherence** is needed to prevent emergence of resistance and maximize viral suppression

*Allows an error rate of 5%:*

- For BID (BD) dosing
  - miss **3 doses** in **1 month** (3 out of 60)
- For TID (TD) dosing
  - miss 5 doses per month (5 out of 90)



# CAN I GET RID OF RESISTANCE ONCE IT DEVELOPS?



- No. Once the HIV in your blood becomes resistant to a certain HIV medication, that med will no longer work the way it should.
- Your second combination of HIV meds **may not work as well** or **last as long** as the first regimen.



# LATENT RESERVOIRS AND RESISTANCE



- ARV resistance, once it develops, is probably lifelong
  - resistant HIV hides in latent cellular reservoirs and can be activated years later
  - i.e., resistant viruses fade but remain “archived”
- Once a person is resistant to an ARV drug, that drug will probably be somewhat ineffective in the future



# CAN A RESISTANT VIRUS BE TRANSMITTED?

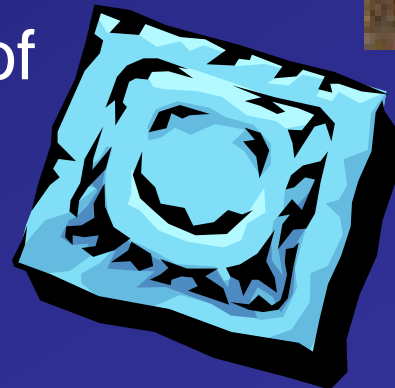


**YES!**

A person with resistant virus can transmit it to another person.

If that person needs to take ARVs, they may not work.

So, even if both members of a couple already have HIV, they should still use condoms.

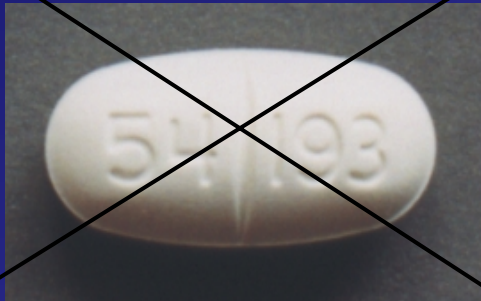




# WHAT IS CROSS-RESISTANCE?



- Some changes can make other ARVs not work, too—even if you've never taken those drugs
- This is because drugs in the same family fight HIV in a similar way
- For example, if you are resistant to nevirapine (NVP), efavirenz (EFV) will also not work





# REMEMBER...BECAUSE THE HIV VIRUS BECOMES RESISTANT...



- “The **first** regimen is the **best** regimen.”
- Important to **minimize the risk** of developing drug resistance in the **first place**
  - Maximize ARV adherence—make it a daily habit!
  - Be knowledgeable about the medications you are taking
  - Utilize a support system of health care providers, family, friends and the community



# SUMMARY



- ARV drug resistance
  - is a consequence of viral replication and
  - can be minimized by **appropriate and regular clinical visits** and **home-based care and support**
  - is an important cause of treatment failure, but other causes must also be considered and ruled out
  - is somewhat preventable
- Excellent adherence is vital



# QUESTIONS?



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