Experiences in HIV Drug and Vaccine Development

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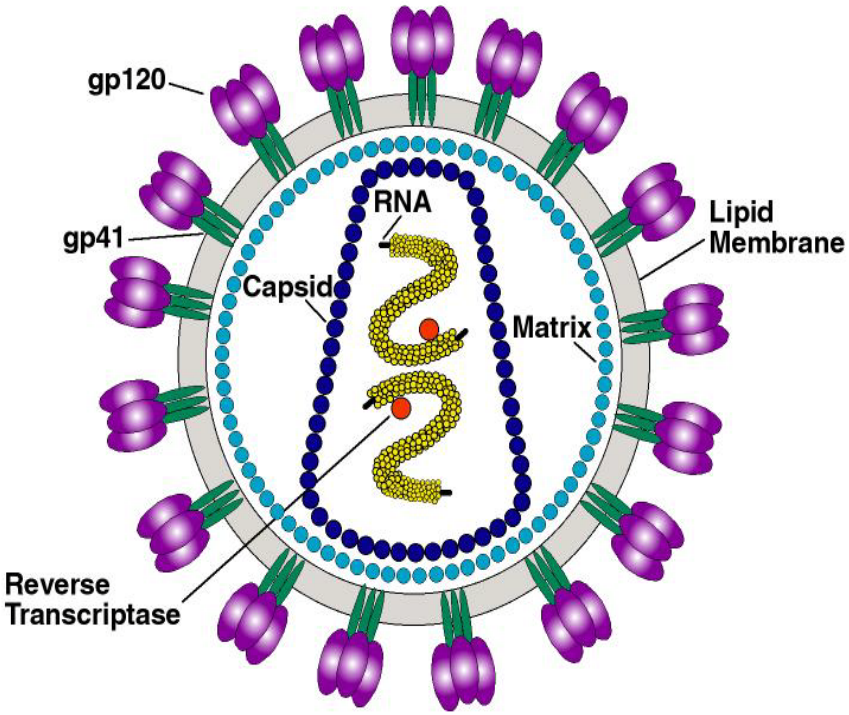
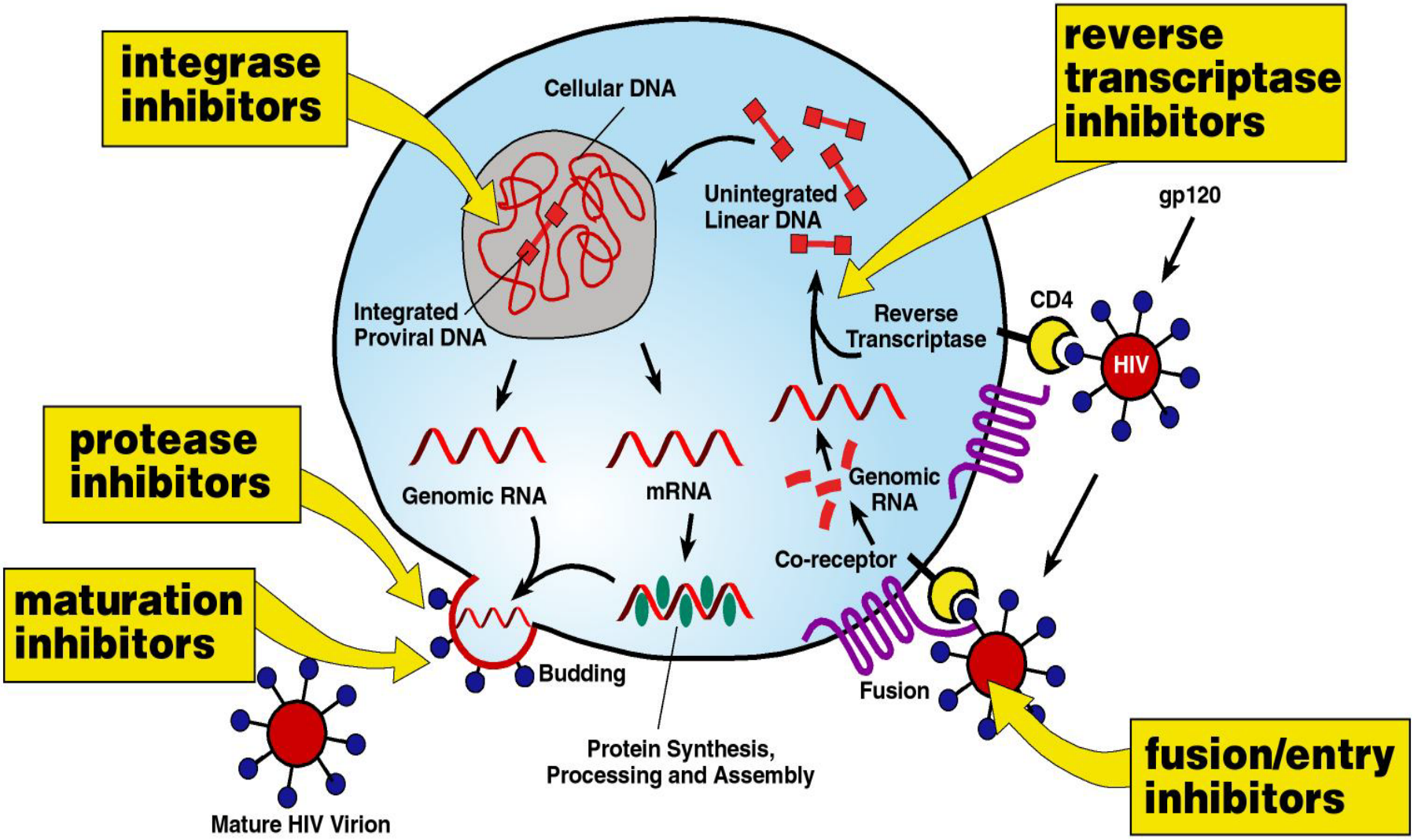
HIV is Different



- The natural immune response to HIV is inadequate
- HIV hides from the immune system
- HIV targets and destroys the immune system
- HIV mutates rapidly

HIV Replication Cycle: Targets for Antiretroviral Therapy



FDA-Approved Antiretroviral Drugs

NRTI

- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

NNRTI

- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine
- Rilpivirine

PI

- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Fusion Inhibitor

- Enfuvirtide (T-20)

Entry Inhibitor

- Maraviroc

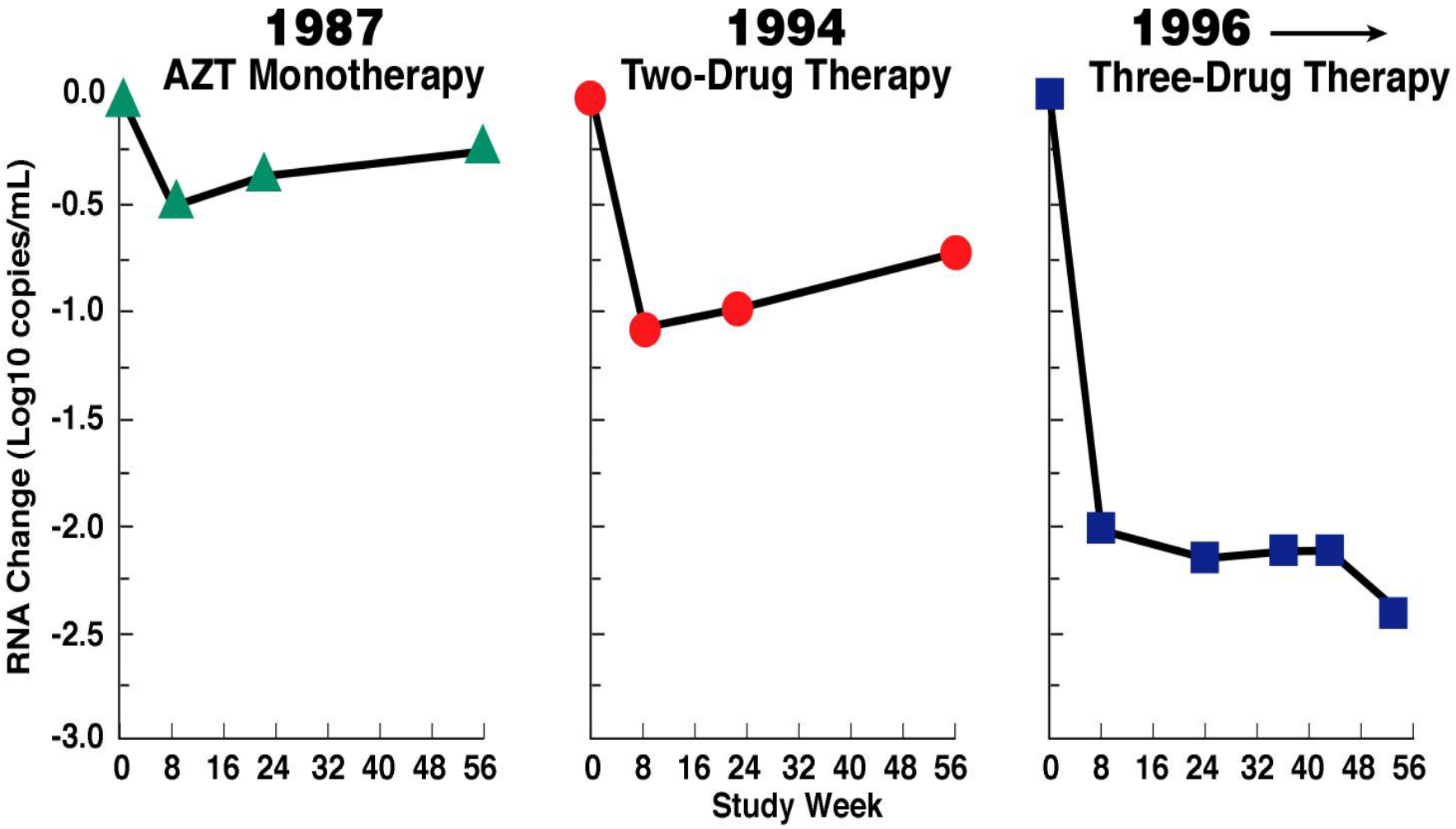
Integrase Inhibitor

- Raltegravir

Combinations

- 6 available, combining 2 or 3 drugs

Evolution of Treatment Strategies for HIV Disease

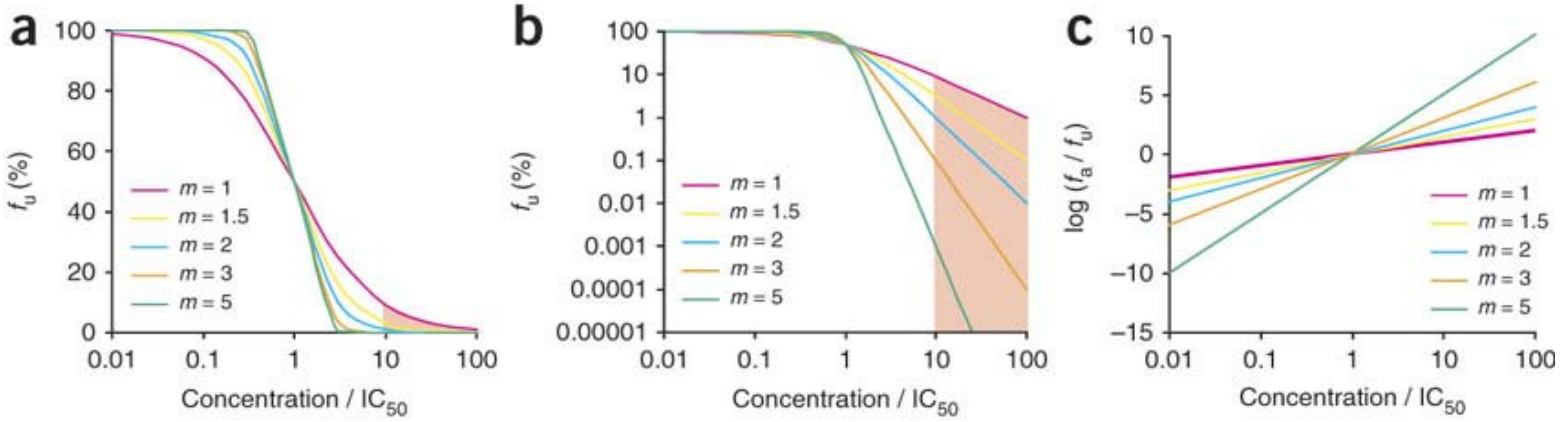


How Are Combinations Chosen?

- **Target at least two steps in lifecycle of HIV**
- **No pharmacological or virological interference**
- **Potency**
- **Safety and side effect profile**
  - Use drugs with least severe effects and combination of drugs should not have overlapping toxicities
- **High genetic barrier to resistance**
- **No pharmacological interference with other medications**
- **Convenience**
  - Once a day dosing preferred
  - Food intake doesn’t matter

A New Approach to Select Combinations

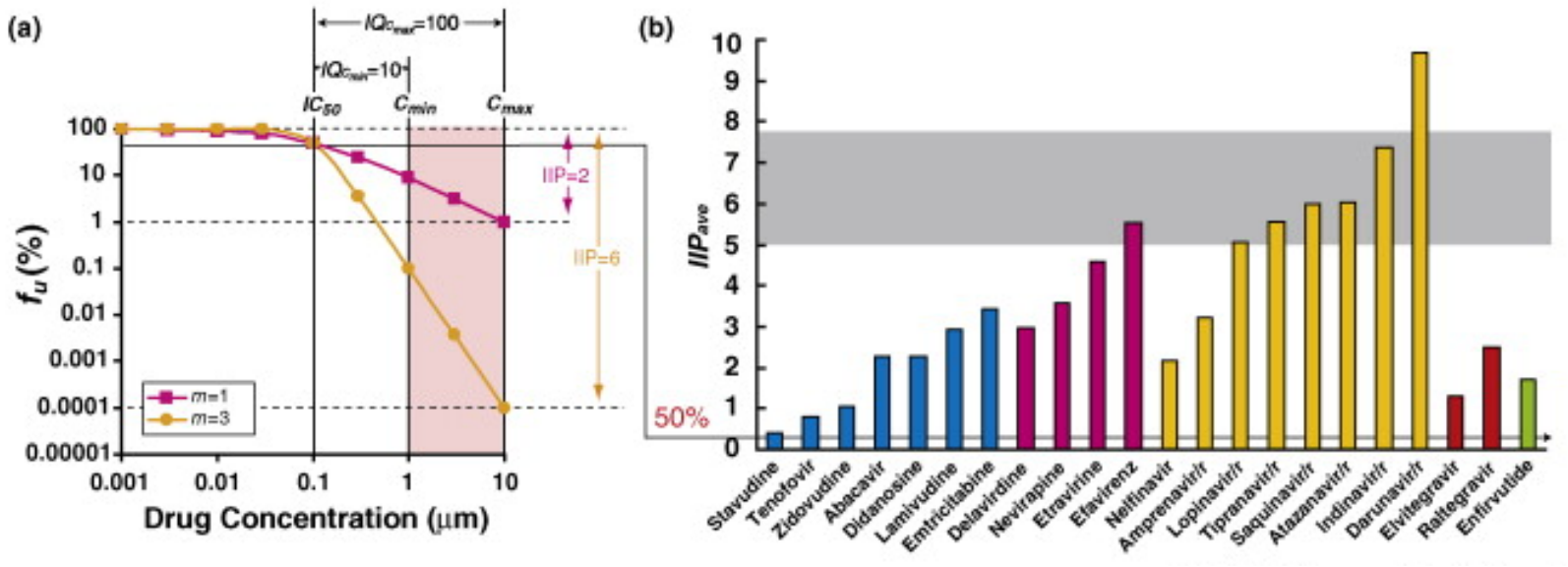
- **The instantaneous inhibitory potential (IIP) is the log reduction in single cycle infectivity at achievable drug concentrations**
- **Each drug class has an IIP based upon the cooperative or non-cooperative nature of drug to target binding**



Shen et al., Nature Medicine 14, 762 - 766 (2008)

A New Approach

- **Minimum IIP needed to block 100% of HIV growth empirically determined**
- **Weakness of 2RT plus and integrase inhibitor regimens predicted by this model**
- **New ART combinations and simpler regimens predicted by this model**



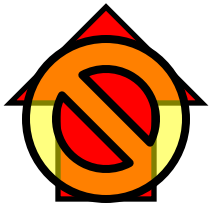
Shen, Rabi and Siliciano Trends in Pharmacological Sciences 2009 30: 610-6

Therapeutic Vaccines for HIV

- **Standard ART is a critical component to suppress virus during immunization period**
- **ART started early to preserve immunity**
- **Effectiveness of current therapeutic vaccines defined by days to rebound after stopping ART**
- **Goal: disease free state in the absence of ART– no HIV progression, no HIV transmission**

Classical Vaccine Design

The response to natural infection provides the proof of concept



HIV Therapeutic Vaccine

(Will require use of standard ART to suppress virus during immunization period)

Questions?

Hepatitis C

- **Telaprevir and Boceprevir approved**
- **PEG IFN plus ribavirin plus Telaprevir signficantly improves response rates**
- **Other classes of direct acting antivirals in clinical development**
- **Goal is potent IFN and Ribavirin-free combination therapy**