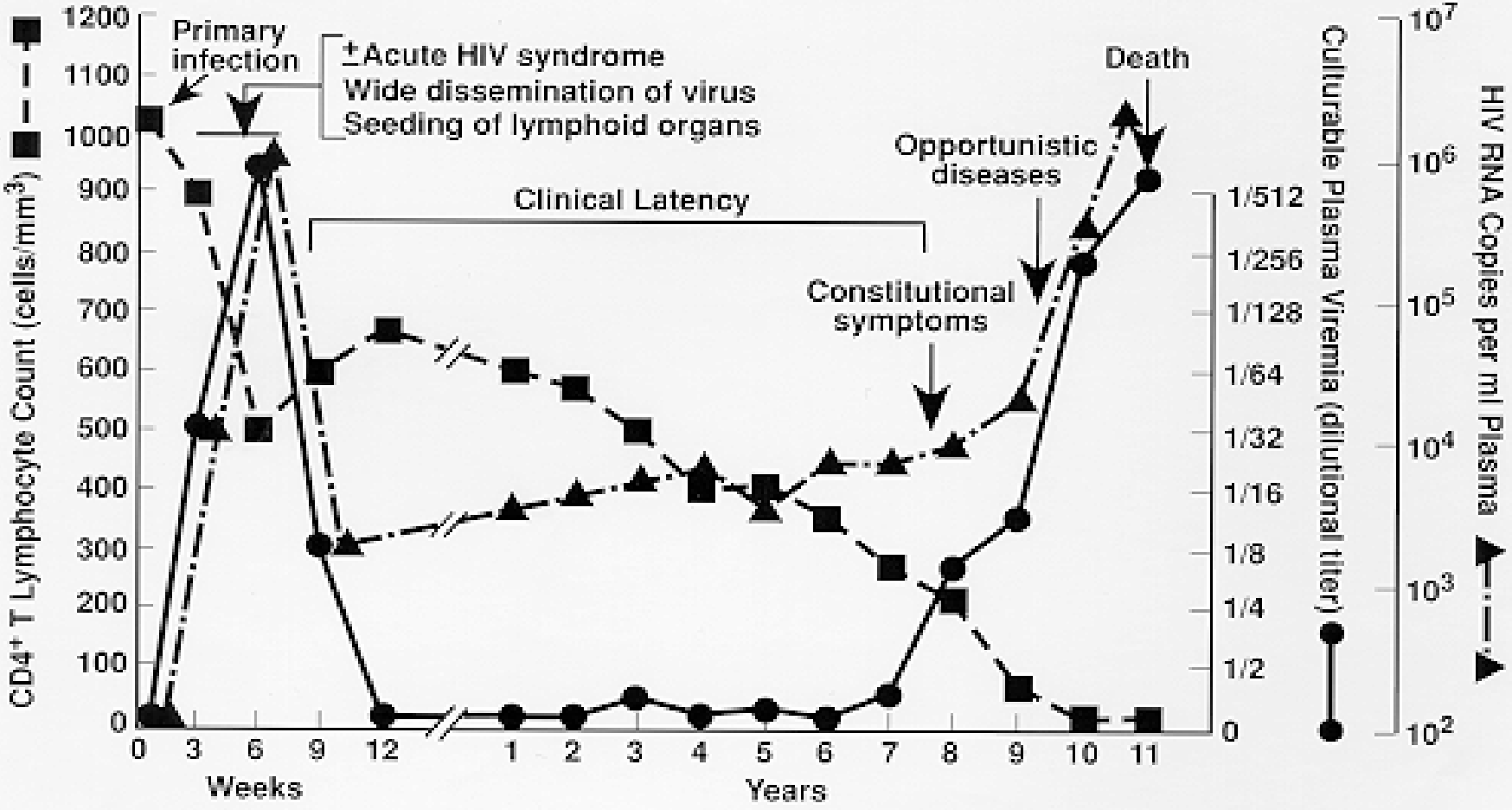
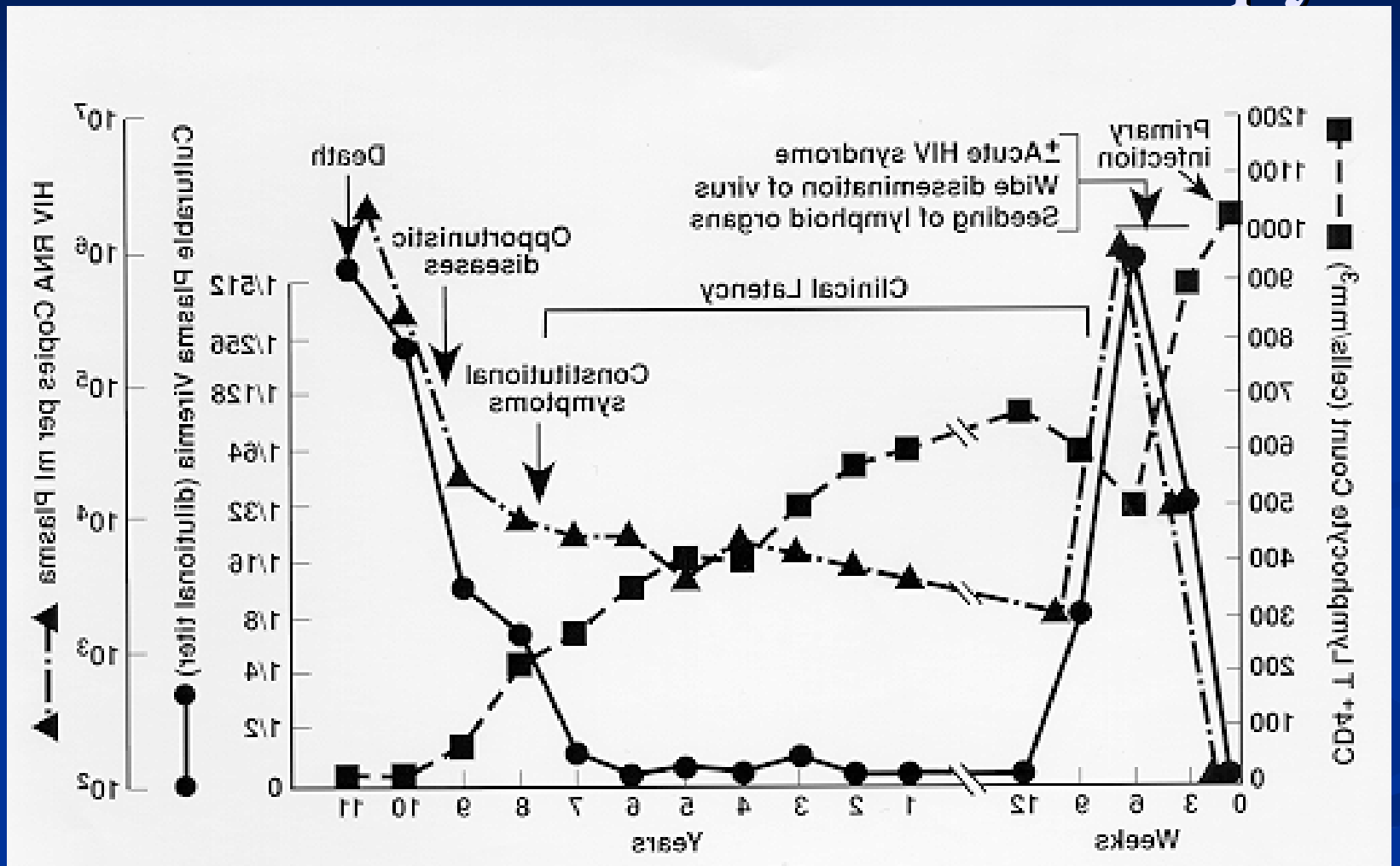
Antiretroviral Therapy: Current Status

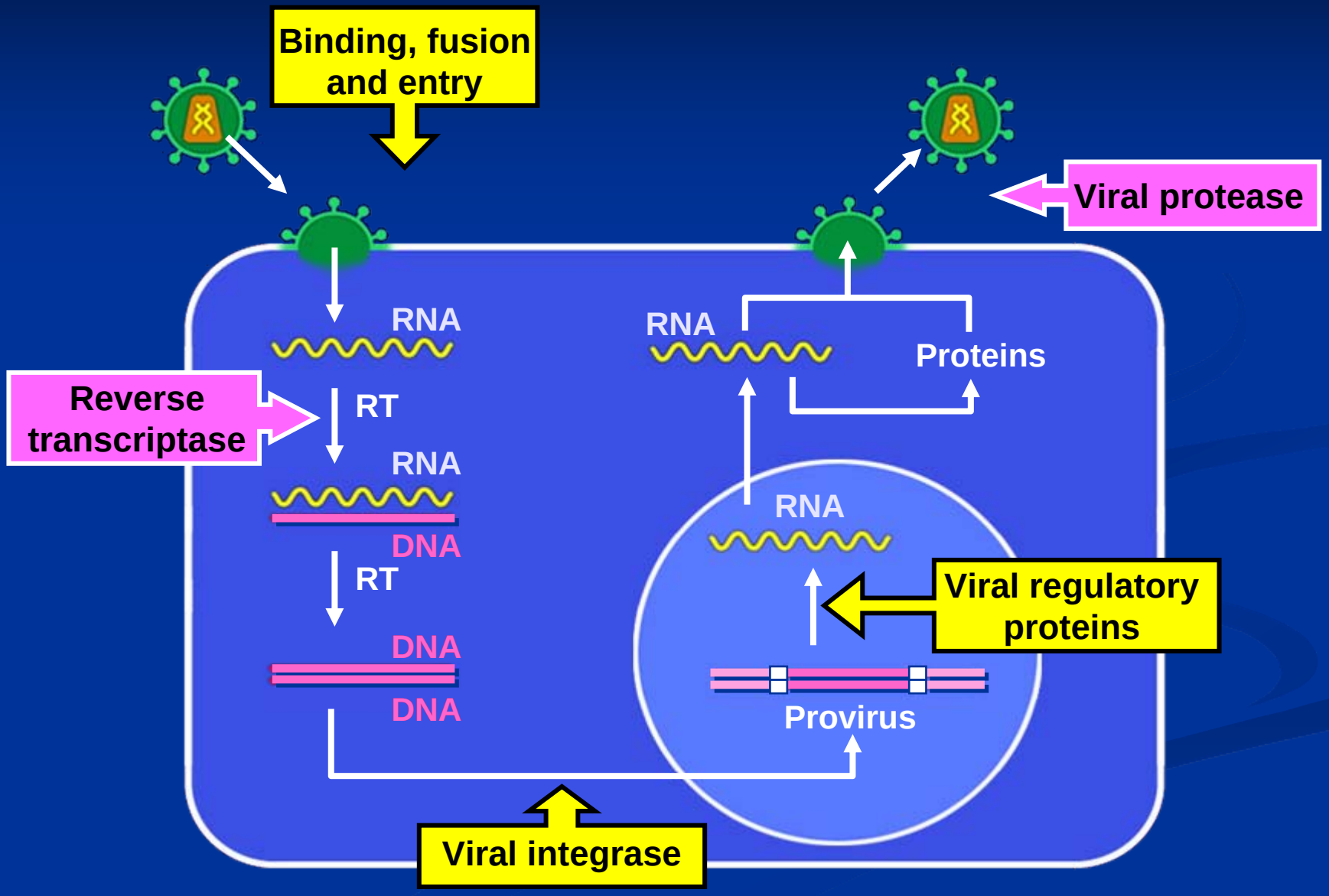
Course of HIV infection



Aim of Antiretroviral Therapy



Potential targets



Currently Available Antiretroviral Medications

Abacavir (ABC)

Didanosine (ddI)

Lamivudine (3TC)

Stavudine (d4T)

Zalcitabine (ddC)

Zidovudine (ZDV)

Emtricitabine (FTC)

Tenofovir (TDF)

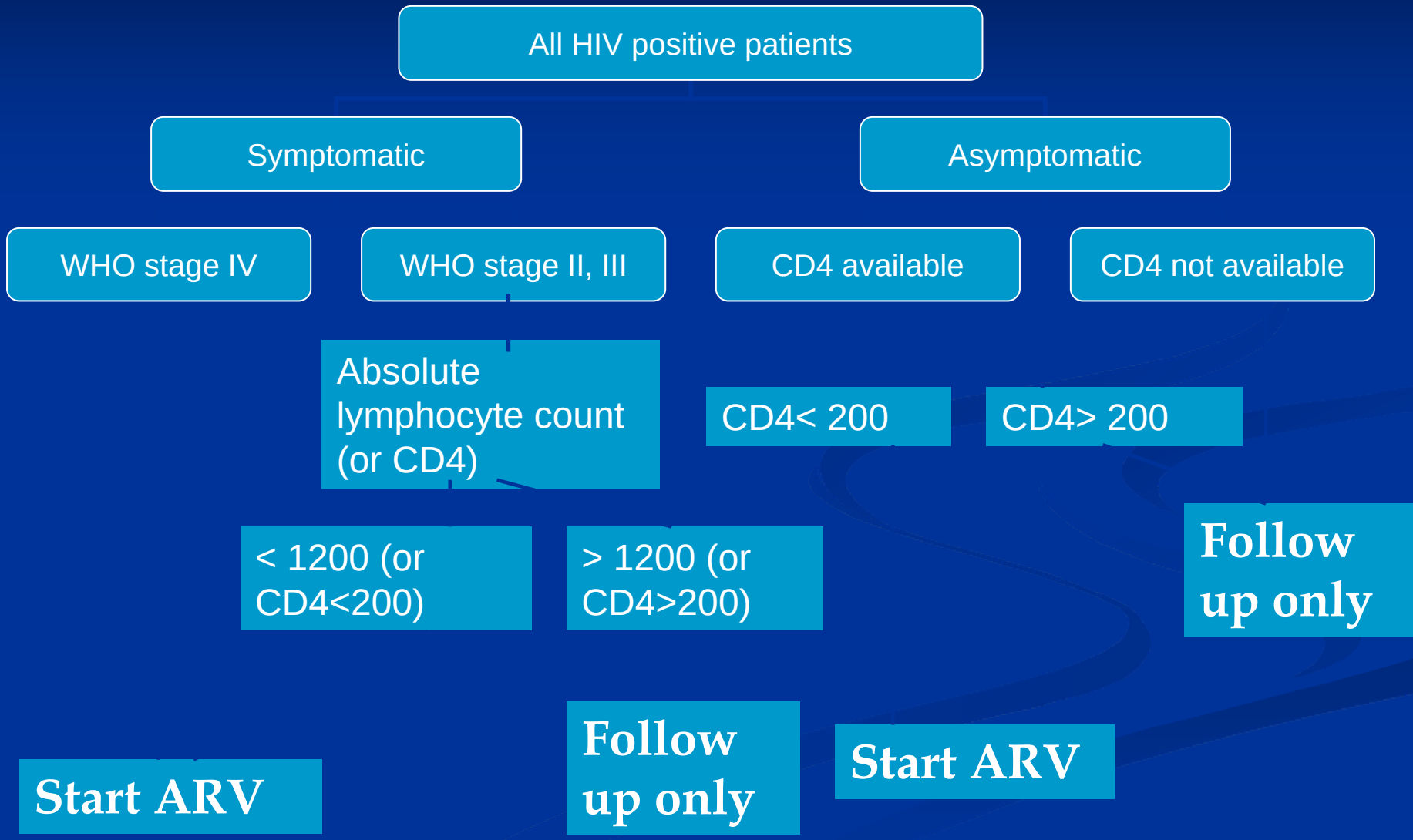
When To Begin - Consensus?

- Patient committed and ready, and one or more..
- High viral load -- increasingly controversial
- CD4 < 350 cells/mm^3 -- increasing consensus
- Symptomatic HIV disease
- Acute and very early HIV infection - duration of therapy unclear, however
- Pregnancy

When Not To Begin

- Patient not committed
- Patient unable to adhere to any regimen
  - Cost of medication; access to refills; lifestyle barriers; psychosocial issues; side effects
- ? During acute OI
- Antiretroviral therapy is a LONG TERM commitment. Do not start it in a hospitalized patient unless there is commitment from the patient about future supplies

How to evaluate and start



WHO recommendations

- In resource restricted settings, adults and adolescents satisfying any of the following criteria can be offered therapy
  - WHO stage IV (clinical AIDS), irrespective of CD4
  - WHO stage I, II or III, if the CD4 is less than 200
  - WHO stage II or III and an absolute lymphocyte count of less than 1200

WHO's recommended second line regimens in adults and adolescents for treatment failure on first line ARV regimen (WHO 2003)

First-line regimen	Second-line regimen
D4T or ZDV	TDF or ABC
+	+
3TC	ddI
+	+
NVP or EV	LVP/r or SQV/r

Indications for Initiation of Therapy: Chronic Infection

Clinical Category	$CD4^+$ T Cell Count	Plasma HIV RNA	Recommendation
Symptomatic (AIDS, severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	<200 cells/μL	Any value	Treat
Asymptomatic	>200 cells/μL but <350 cells/μL	Any value	Treatment should be offered, with consideration of pros and cons

Indications for Initiation of Therapy: Chronic Infection

Clinical Category	$CD4^+$ T Cell Count	Plasma HIV RNA	Recommendation
Asymptomatic	>350 cells/μL	>100,000 copies/mL	Most clinicians recommend deferring therapy; some will treat
Asymptomatic	$CD4^+$ T cells >350 cells/μL	<100,000 copies/mL	Defer therapy

Antiretroviral Medications: Should not be offered at any time

- Regimens not recommended:
  - Monotherapy (except possibly in prevention of perinatal HIV transmission)
  - Dual NRTI therapy
  - 3-NRTI regimen of abacavir + tenofovir + lamivudine
  - 3-NRTI regimen of didanosine + tenofovir + lamivudine

Antiretroviral Medications: Not offered at any time

- Antiretroviral components not recommended:
  - Didanosine + stavudine
  - Stavudine + zidovudine
  - Emtricitabine + lamivudine
  - Zalcitabine + stavudine; zalcitabine + didanosine; zalcitabine + lamivudine

Antiretroviral Medications: Not offered at any time

- Antiretroviral components not recommended:
  - Efavirenz in pregnancy and in women with high potential for pregnancy*
  - Nevirapine initiation in women with CD4 >250 cells/mm3 or men with CD4 >400 cells/mm3

Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTI's)- I

	Zidovudine (AZT)	Didanosine (ddI)	Zalcitabine (ddC)
Dose			
Food			
Adverse Events			

Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTI's)- I

	Zidovudine (AZT)	Didanosine (ddI)	
Dose			
Food			
Adverse Events			

Characteristics of NRTI's – II

	Stavudine (d4T)	Lamivudine (3TC)	Abacavir (ABC)
Dose			
Food			
Adverse Events			

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

	Nevirapine	Delavirdine	Efavirenz
Dosing			
Food Effects			
Adverse Events			

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

	Nevirapine		Efavirenz
Dosing			
Food Effects			
Adverse Events			

Protease Inhibitors - I

Name	Indinavir	Ritonavir	Nelfinavir
Dose	800 mg q8h. Separate dosing with didI by 1 hr	600 mg q 12h. Separate dosing with didI by 2 hrs	750 mg tid or 1250 mg bid
Food			
Side Effects			

Protease Inhibitors - II

Name	Saquinavir		Lopinavir + Ritonavir
Dosing			
Food Effect			
Side Effects			

Protease Inhibitors - II

Name	Saquinavir	Amprenavir	Lopinavir + Ritonavir
Dosing			
Food Effect			
Side Effects			

Adverse Effects: NRTIs

- Abacavir - hypersensitivity reaction, lactic acidosis (LA)
- Didanosine - GI intolerance, pancreatitis, peripheral neuropathy (PN), LA
- Stavudine - PN, LA, pancreatitis
- Tenofovir - HA, GI
- Zalcitabine - PN, LA
- Zidovudine - HA, GI, LA, bone marrow suppression

- Pregnant women may be at increased risk for lactic acidosis and liver damage when treated with the combination of stavudine and didanosine. This combination should be used in pregnant women only when the potential benefit clearly outweighs the potential risk.

Adverse Effects: NNRTIs

- Nevirapine - rash, hepatitis
- Efavirenz – rash, CNS, teratogenic in primates

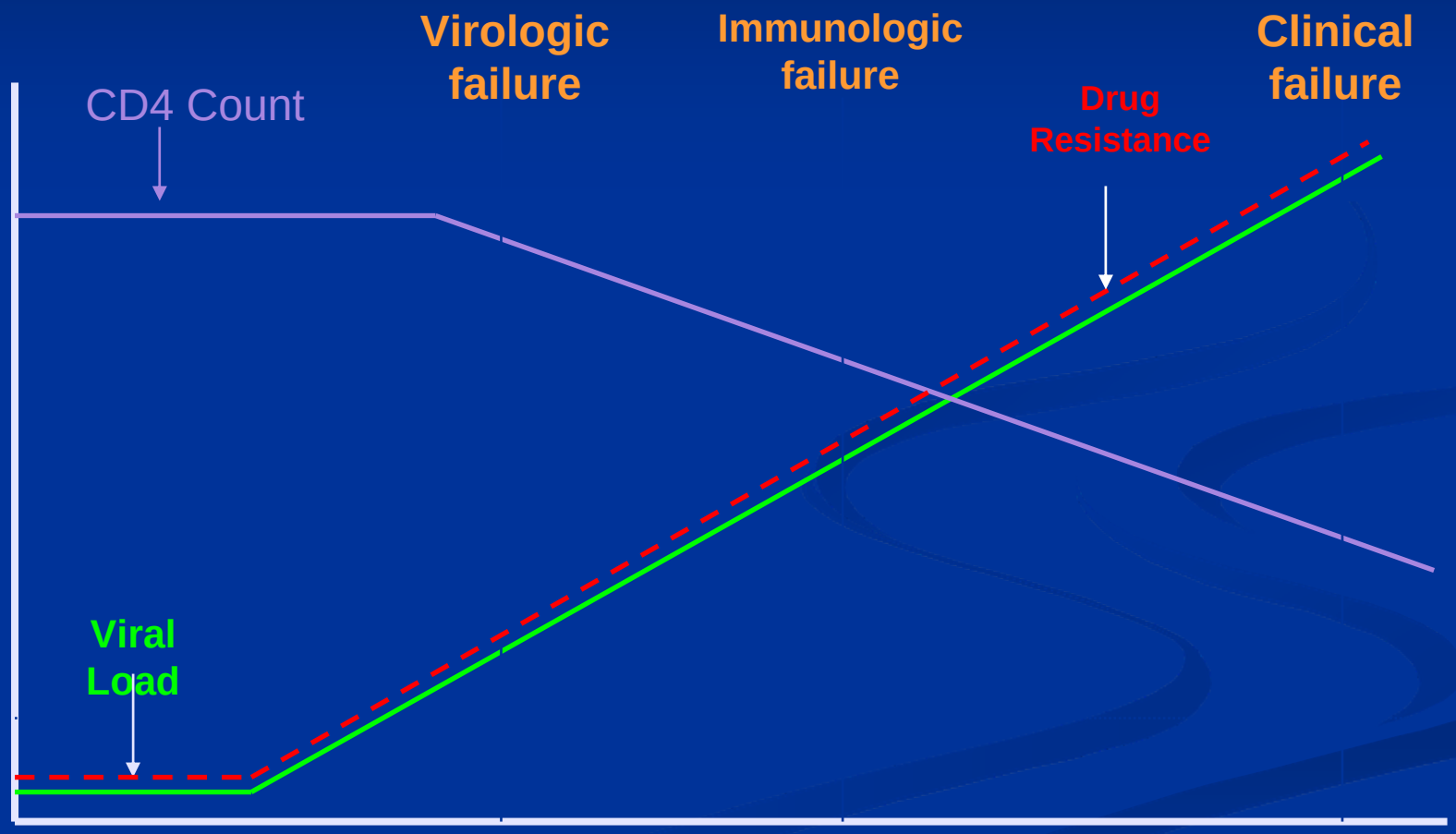
Adverse Effects: PIs

- Indinavir – nephrolithiasis, GI intolerance
- Ritonavir - GI intolerance, hepatitis
- Nelfinavir - diarrhea
- Amprenavir - GI intolerance
- Lopinavir + Ritonavir – GI intolerance
- All PIs:
  - Insulin resistance and diabetes
  - Fat redistribution
  - Hyperlipidemia

HAART - Long Term Concerns

- Long term risk of toxicity
  - described
  - not yet described
- Durability of suppression unknown
- Current options are limited
- Future options uncertain
- Adverse effects difficult to predict
- Adherence difficult to predict
- Response in any individual difficult to predict
- Criteria for when to change, how to sequence ARV Rx inadequately characterized

Treatment Failure and Drug Resistance



When to Switch: First HAART

- There are few data that provide the optimal point (e.g., any detectable viral load, > 500 copies/mL, > 1000 copies/mL) at which therapy should be changed . . . . the major short-term risk of any level of viral replication in the presence of antiretroviral therapy is emergence of resistance.

Treatment-Experienced Patients: Treatment Regimen Failure

- **Virologic failure:**
  - HIV RNA >400 copies/mL after 24 wks, >50 after 48 wks, or >400 after viral suppression
- **Immunologic failure:**
  - CD4 increase of less than 25-50 cells/mm^3 in first year of therapy
- **Clinical failure:**
  - occurrence of HIV-related events (after >3 months on therapy; excludes immune reconstitution syndromes)

Changing Therapy: Considerations for Toxicity

- For toxicity known to be due to single agent, single agent substitution
- For toxicity that can't be ascribed to single drug that is severe enough to warrant discontinuation, all agents should be stopped; introduce new regimen after resolution of toxicity
  - Staggered discontinuation of drugs with different half-lives should be considered to avert resistance; but clinical relevance unknown

Changing Therapy: Considerations for Toxicity (cont'd)

- For PI-associated lipid abnormalities, manage abnormalities if benefit of maintaining PI outweighs risk of changing
  - If drug-susceptible virus at baseline, switch to NNRTI can be considered
- For fat maldistribution syndromes, early switching of responsible drug(s) is recommended if drug options exist

Changing Therapy: Considerations for Treatment Failure—First Regimen Failure

- Adherence, adherence, adherence
- First regimen failure
  - Resistance testing for plasma viral load >500 to 1000 HIV RNA copies/mL
  - Alter regimen if resistance is documented
  - Target for new therapy is <50 copies/mL (below detection)

Conclusions: Multiple HAART Failure

- Disease progression is delayed in presence of MDR vs. wild-type HIV
  - Mechanism not clear
- Strategies that select for viruses with reduced "fitness" may result in lower viral loads and delayed progression
  - 3TC, tenofovir, most protease inhibitors
- Fitness and "pathogenicity" are unique phenomena
  - Are protease inhibitors required to achieve durable clinical benefit if face of MDR?
  - Will disease stage/co-infections impact on this?

Monitoring Antiretroviral Therapy

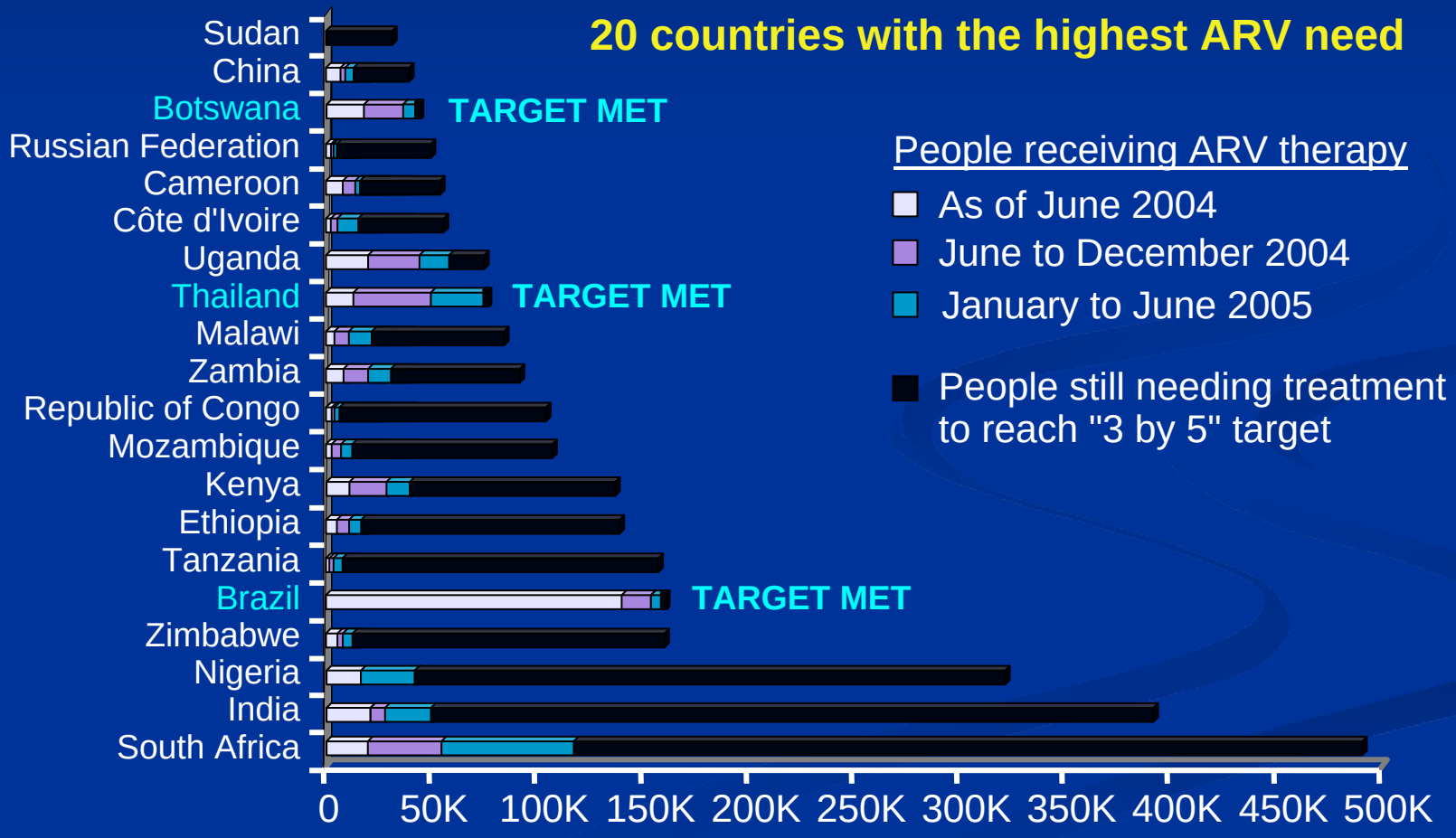
- "Blips" in viral load are not a reason to change drugs
- If adverse effect or ineffective suppression, recommend

Problems with therapy

- Optimum duration?
- Regimens are complex & may involve intake of more than 10 pills/day
- Cost of currently available drugs + cost of lab tests
- IRIS
- Drug resistance

31st Dec ‘05 60 centers &
21,318 patients on ART

3X5



Conclusions

- ART remains a rapidly evolving and challenging area of medicine
- The field will continue to evolve with additional insights into pathogenesis and new drug development
- New agents in existing classes and in new classes (eg, CCR5 inhibitors, integrase inhibitors, maturation inhibitors) that have reached clinical testing provide hope that new treatment options will be available in the next few years

All the best..