Critical Issues in Antiretroviral Therapy

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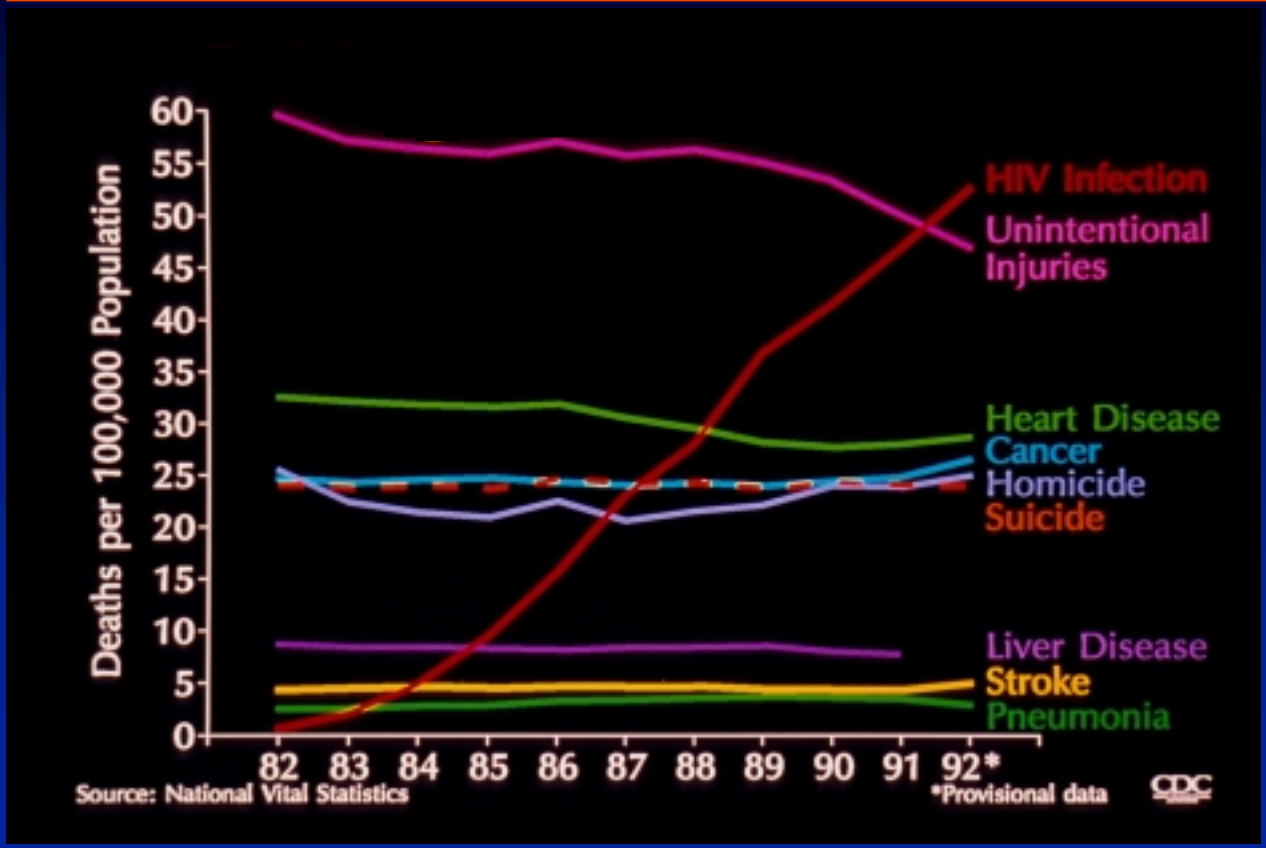
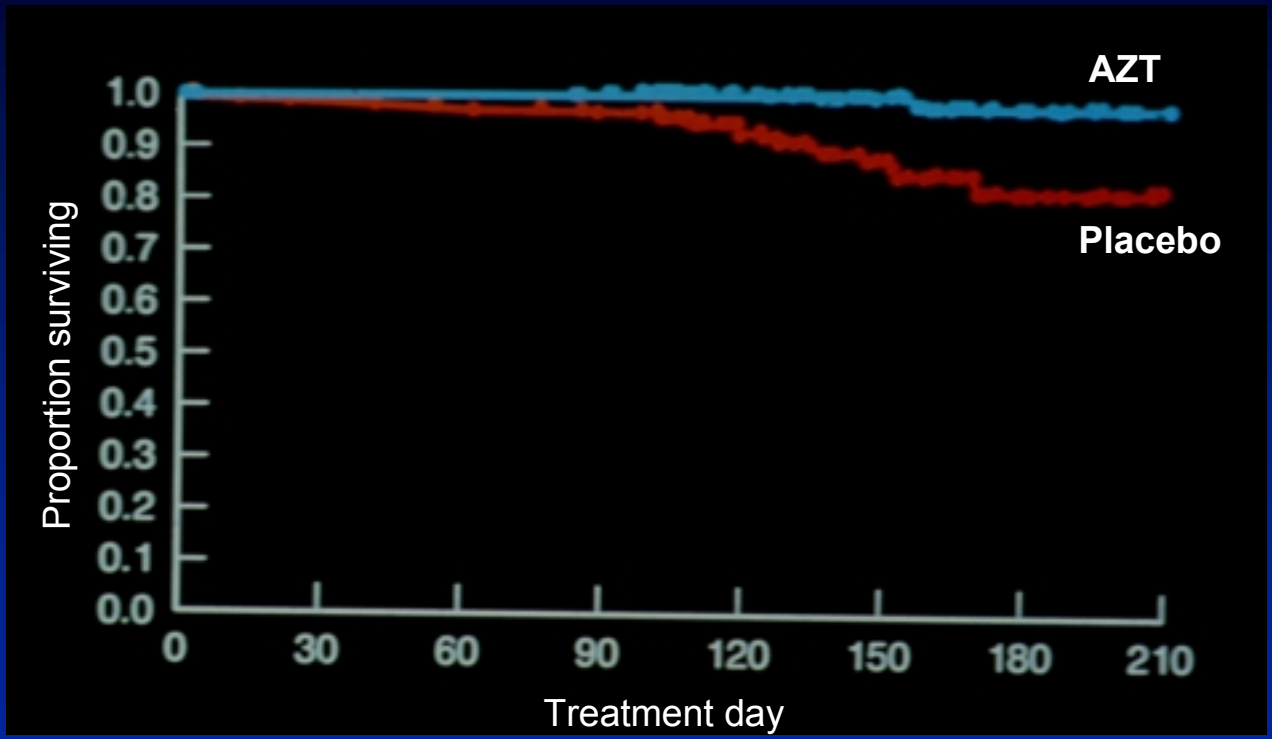
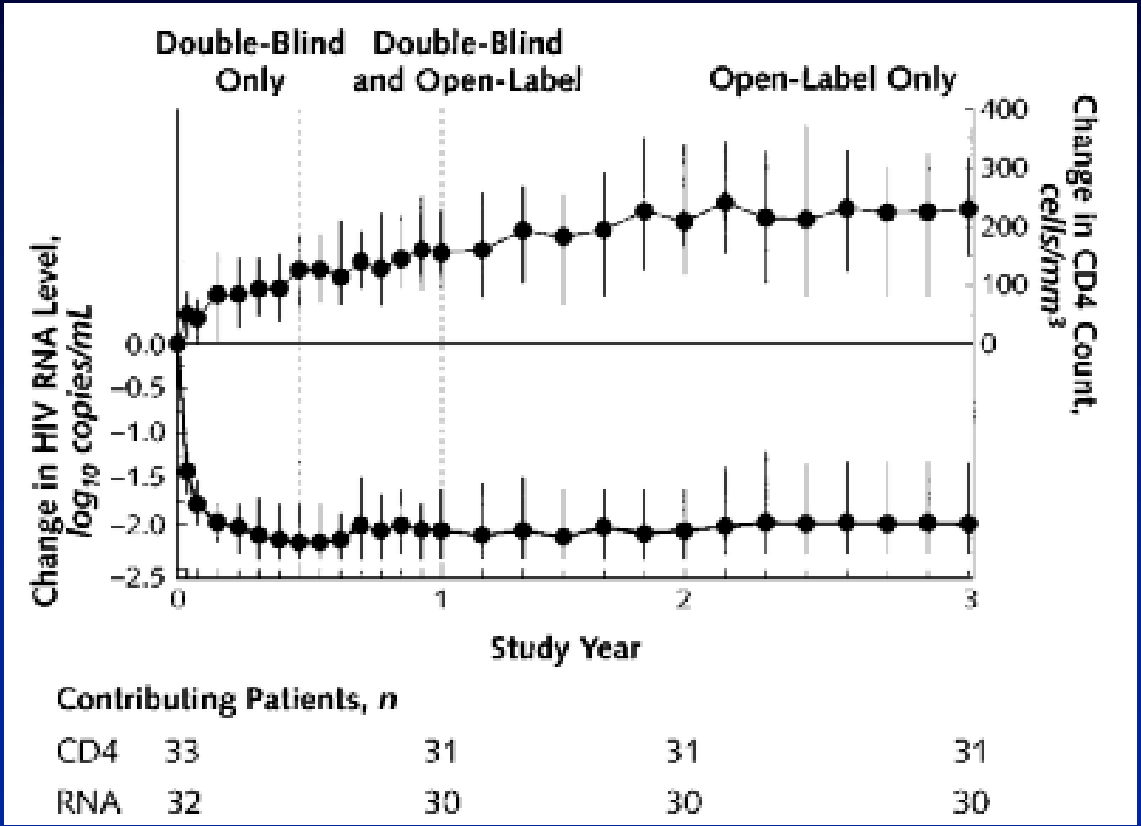
HIV-associated mortality in US men aged 25-44 years (1982-92)



Survival in BW-02 study of AZT

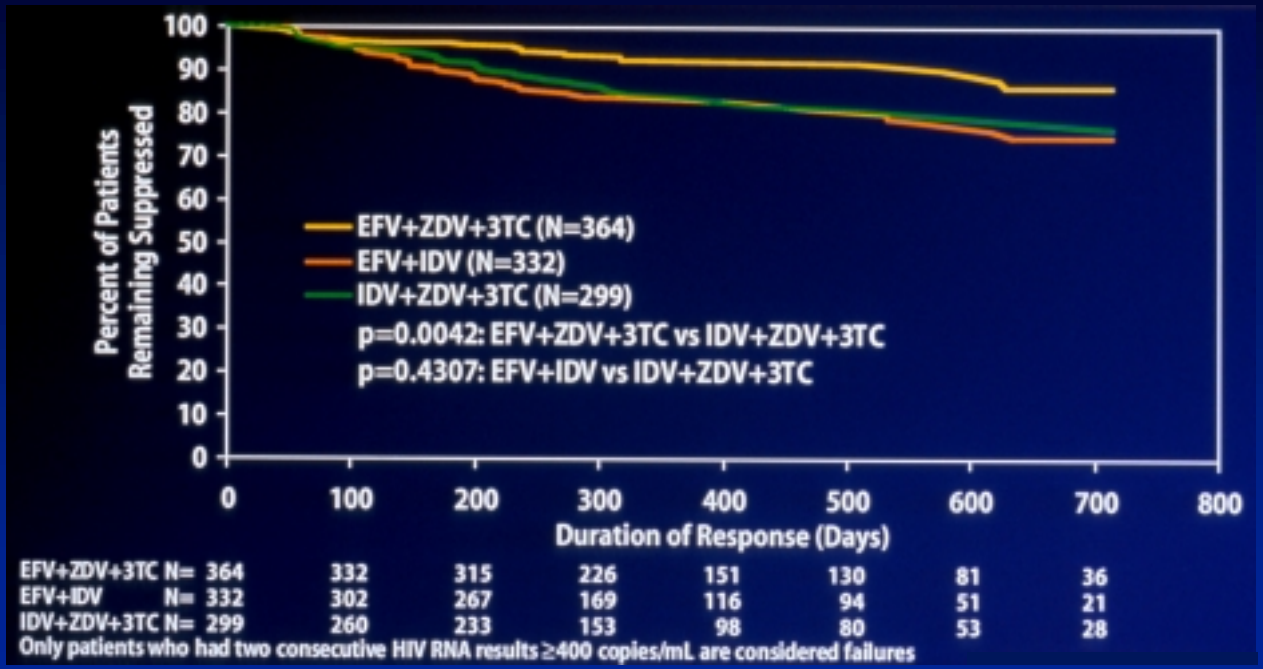


Merck 035: 3-year follow-up of patients treated with AZT/3TC/IDV



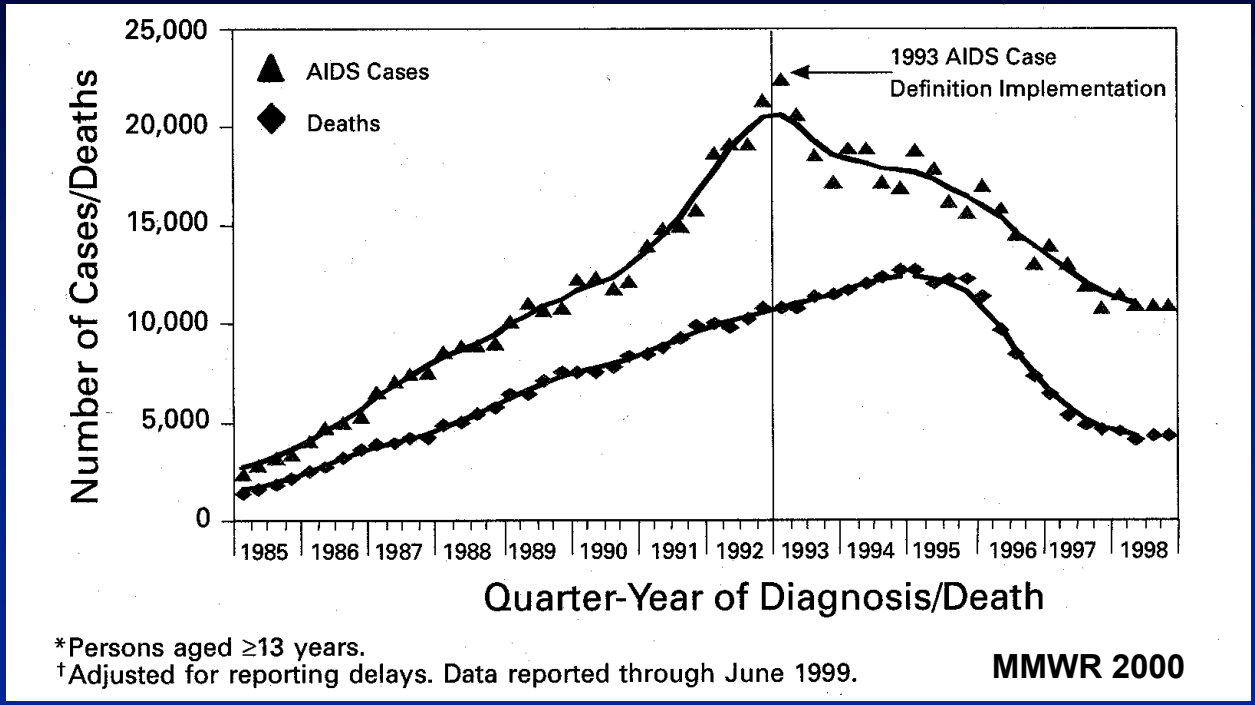
Gulick et al. Ann Intern Med 2000

EFV 006: Time-from-response analysis (virologic failure endpoint)



Staszewski et al 39th ICAAC 1999.

US AIDS incidence 1985 - 1998



*Persons aged ≥13 years.
†Adjusted for reporting delays. Data reported through June 1999.

MMWR 2000

Goals of antiretroviral therapy

- Delay disease progression and prolong survival
- Suppress HIV-1 replication
- Preserve or restore immune function
- Minimize toxicity
- Prevent emergence of drug-resistant virus

Limitations current therapy

- Toxicity
- Complexity
- Cost
- Resistance

New “complications” of HIV infection

- **Hyperlipidemia**
  - Triglycerides
  - cholesterol
- **Fat atrophy/deposition**
  - “lipodystrophy”
- **Insulin resistance**
  - Syndrome X
- **Mitochondrial toxicity (?)**
  - peripheral neuropathy
  - pancreatitis
  - lactic acidosis

Unresolved questions in HIV treatment

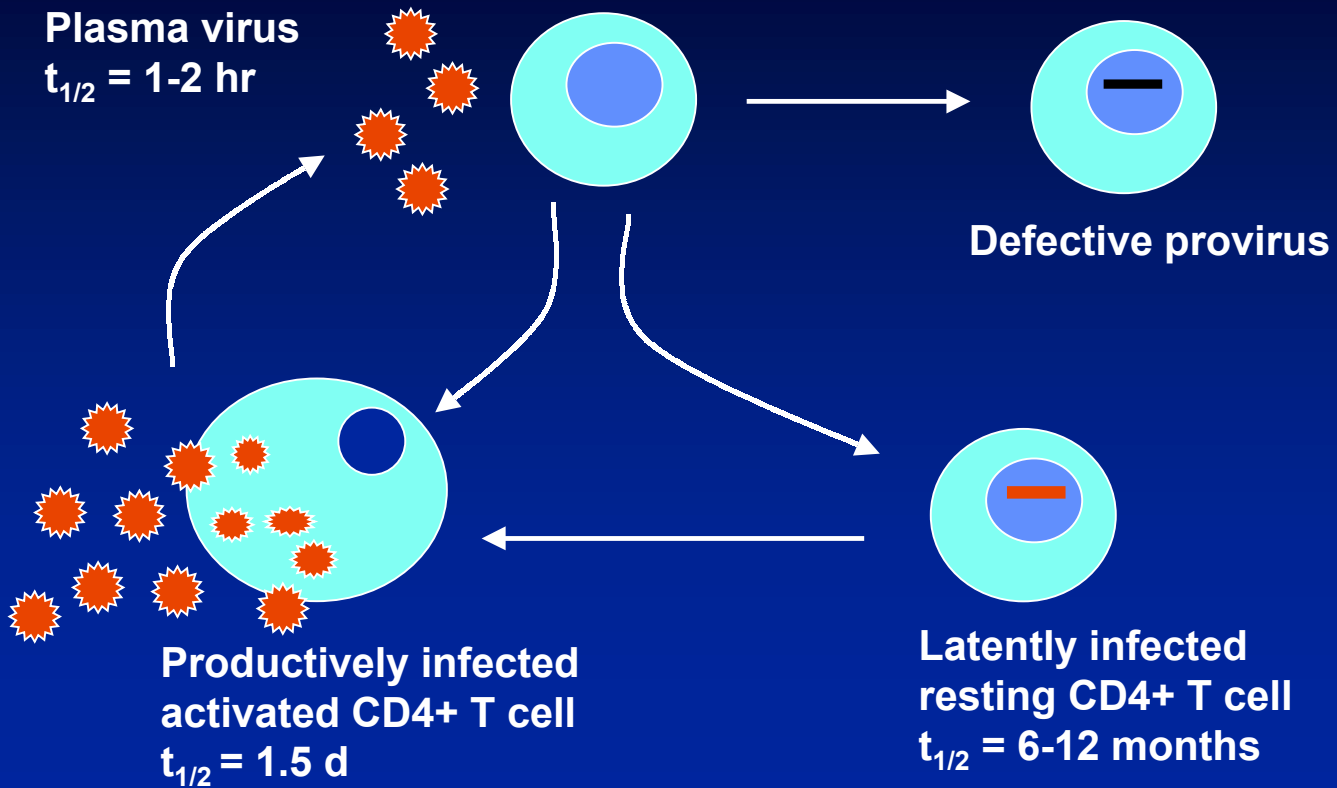
- When to start therapy?
- What to start with?
- When to switch (what is failure)?
- How to use resistance testing?
- How to manage/prevent metabolic toxicities?

Critical Issues in Antiretroviral Therapy

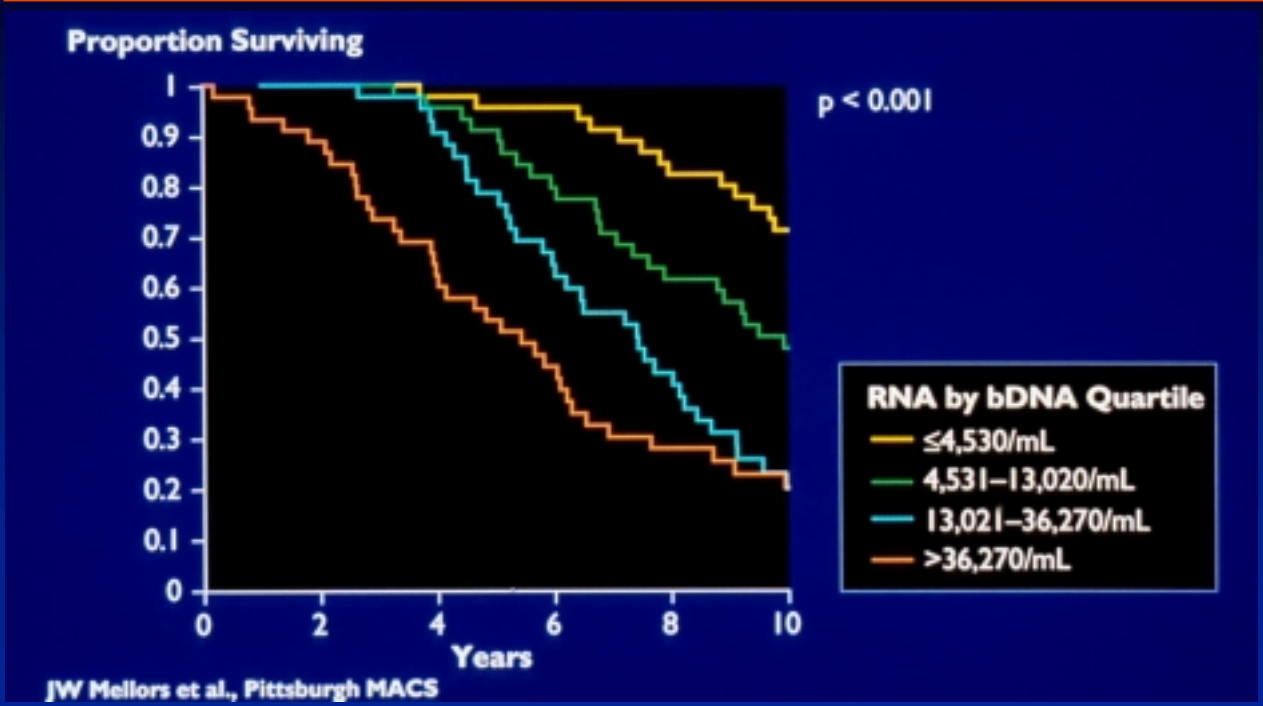
- Viral reservoirs
- “Discordant” immunologic responses in patients with treatment failure
- Treatment interruption

Viral Reservoirs

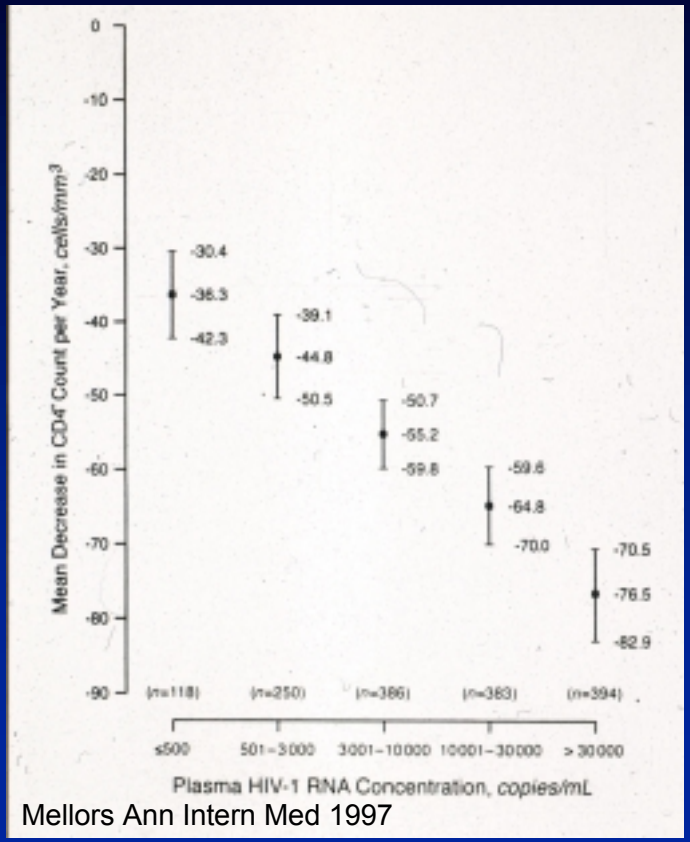
Dynamics of HIV-1 infection



Baseline HIV-1 RNA and survival

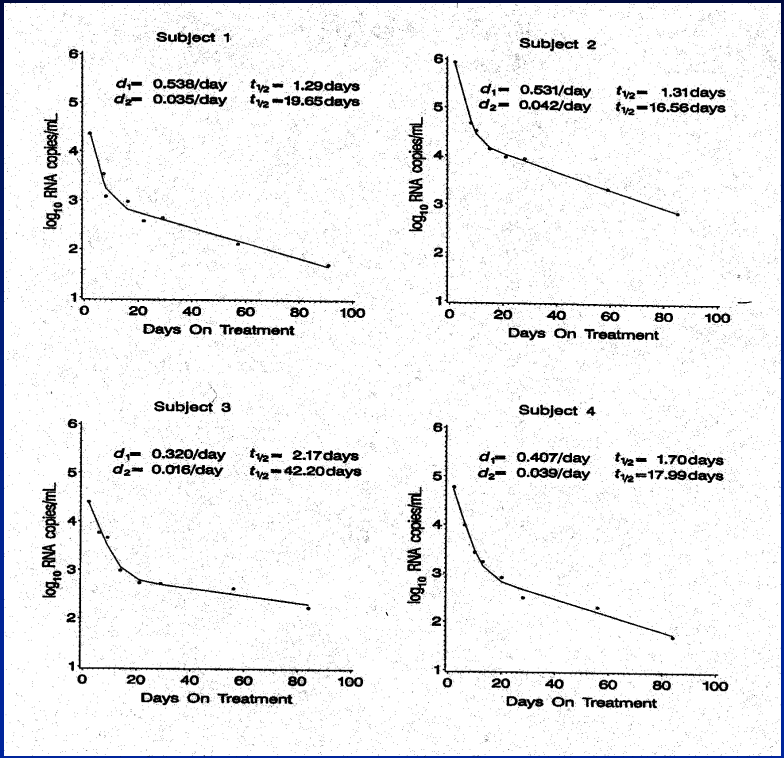


Correlation of plasma HIV-1 RNA level with rate of CD4 count decline



Mellors Ann Intern Med 1997

Viral dynamics:illustrative patterns

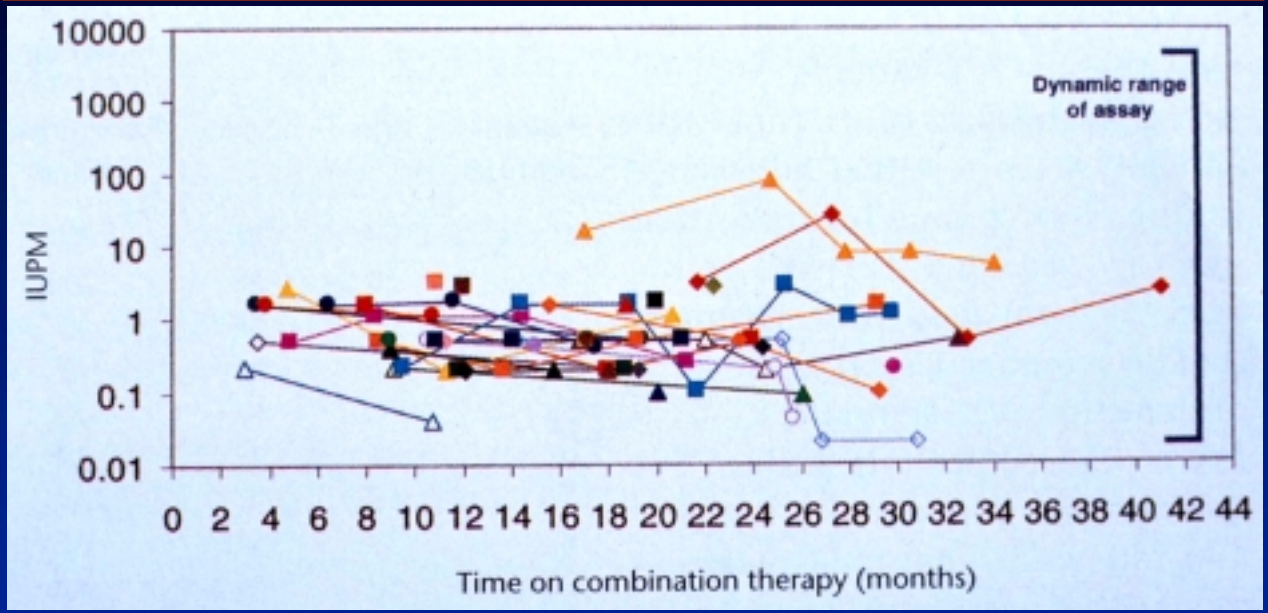


Wu et al J Infect Dis 1999;179:799-807.

Latent reservoirs of HIV-1

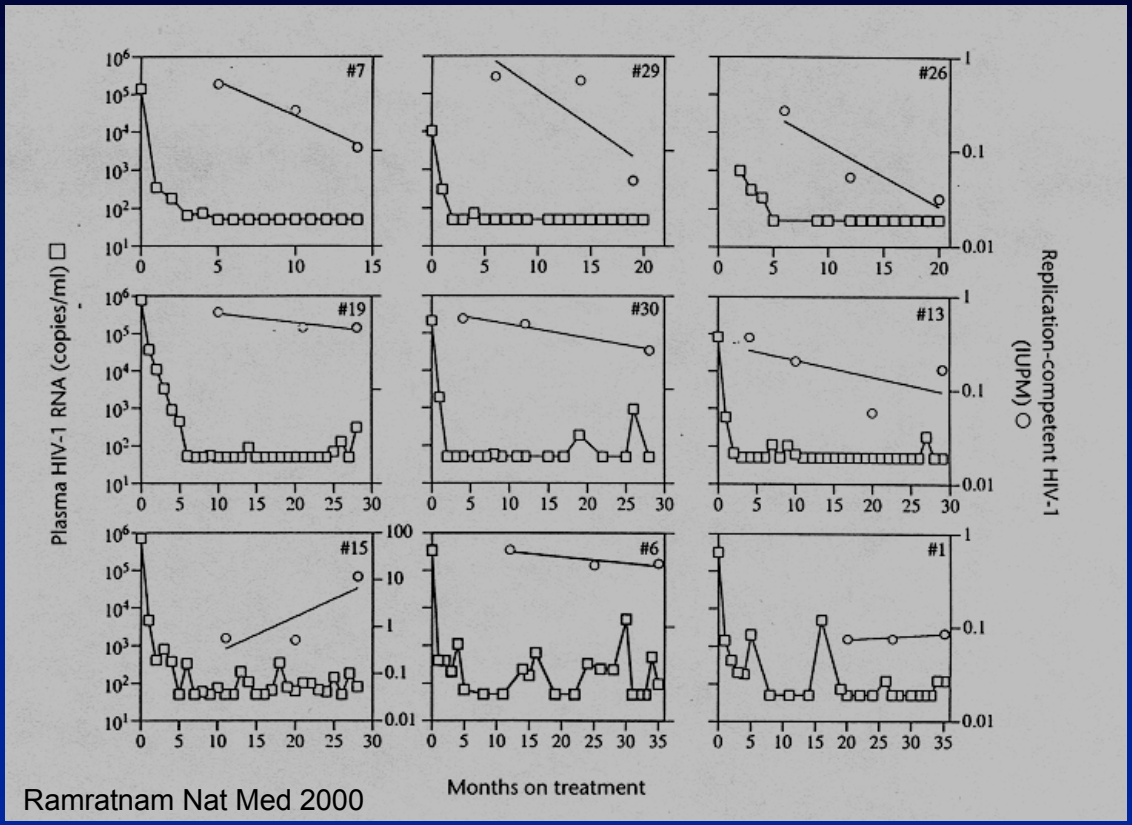
- Established early in infection
- Small
  - (estimated pool size $<10^6$ cells)
- Slow to decay

Persistence of replication-competent HIV-1 in resting CD4+ memory cells



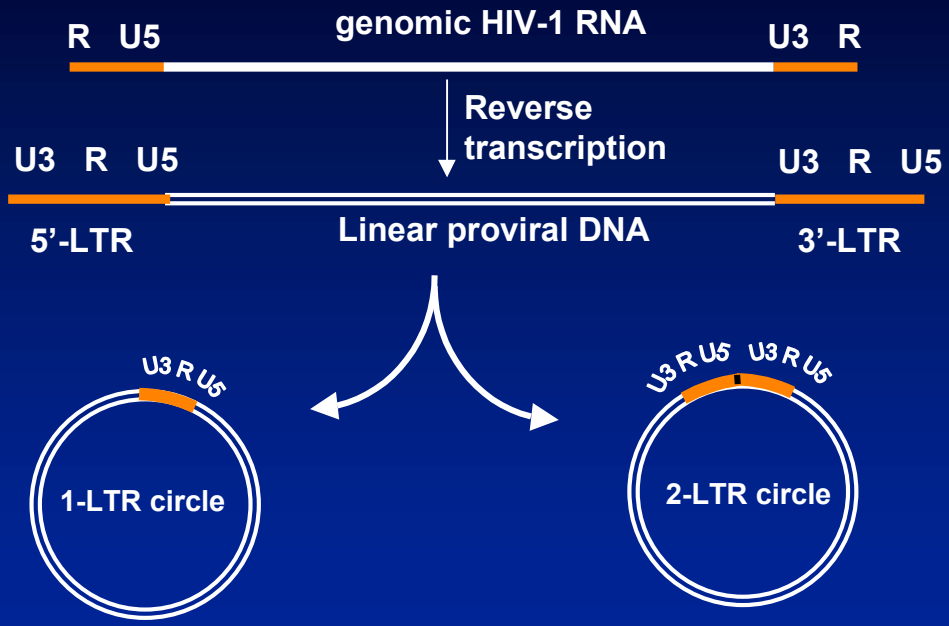
Finzi et al Nat Med 1999

Decay of latently infected PBMC

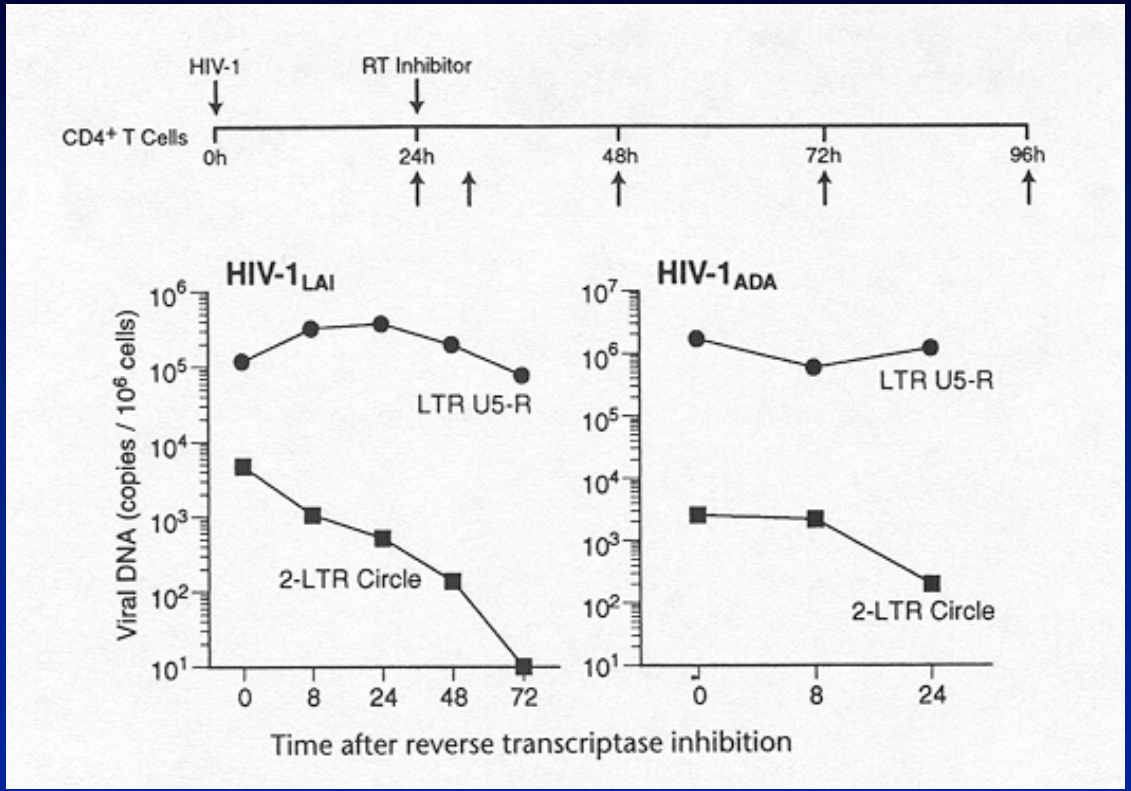


Ramratnam Nat Med 2000

2-LTR circles

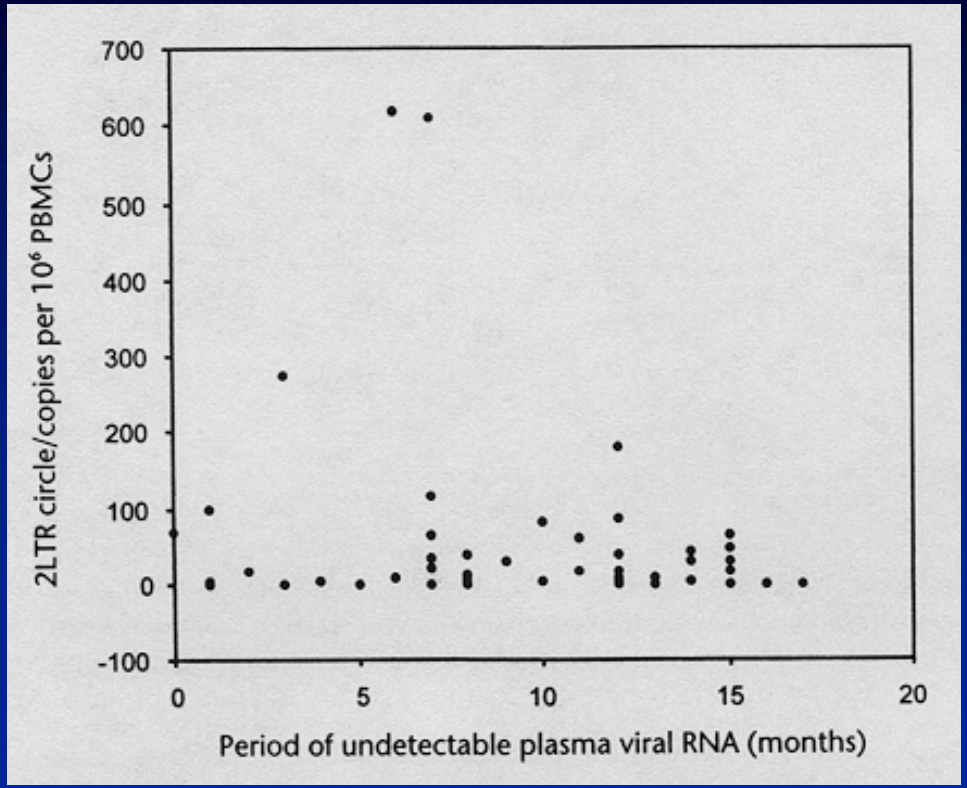


Stability of 2-LTR circles in vitro



Sharkey et al Nat Med 2000

2-LTR circle titer vs time undetectable



Questions regarding viral reservoirs

- **Does evidence for persistent replication of drug-sensitive virus imply the existence of drug sanctuaries?**
  - Anatomic
  - Cellular (transport; activation)
- **Why does replicating virus remain "contained"?**
  - Effective immune control?
  - Limited pool of susceptible host cells?
- **What are the long-term clinical implications of low-level persistent replication?**
  - Does persistent replication forecast ultimate relapse?
  - When? After how many months/years of Rx?

Treatment implications

- More potent drugs?
- More aggressive therapy?
- Drugs targeted to specific reservoirs?
- Can the reservoir be purged?

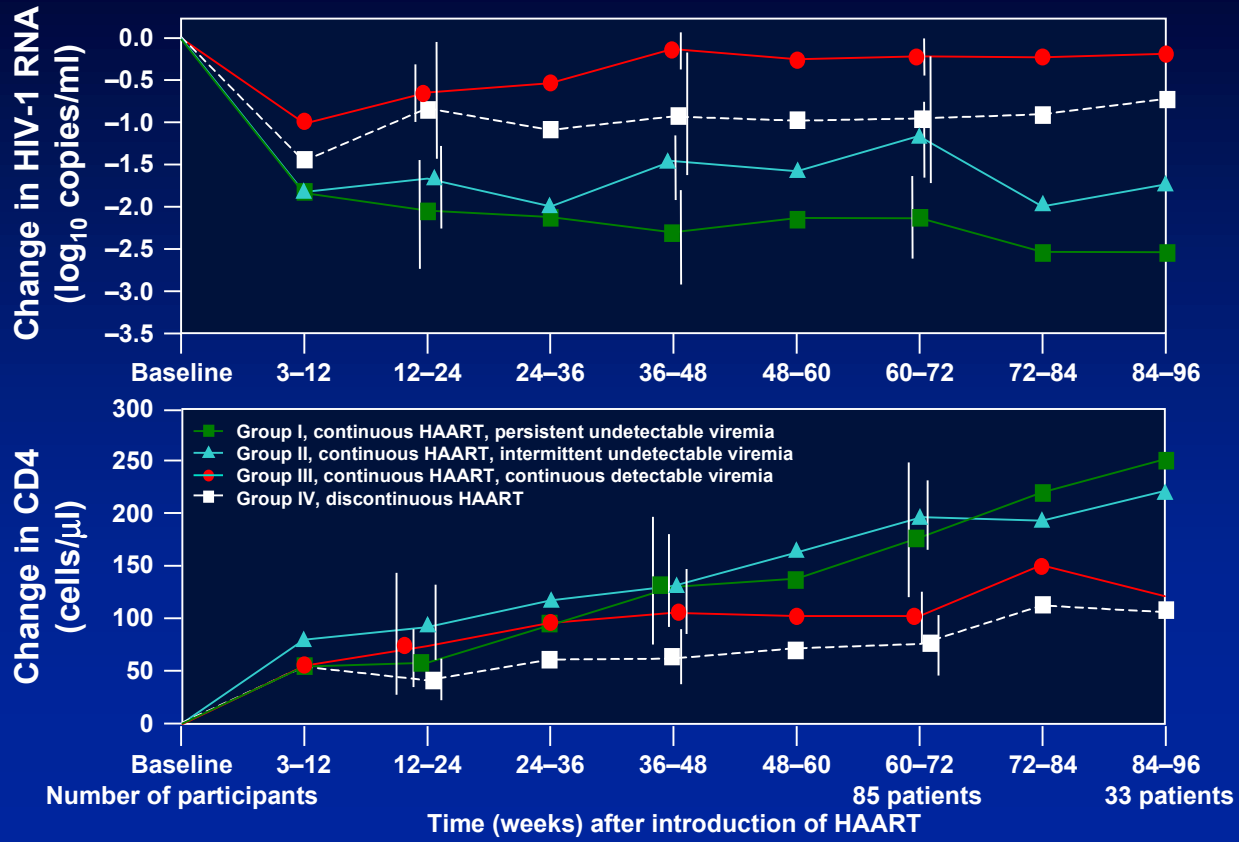
What is failure?

Do “blips” matter?

- **Presence of intermittent viremia does not predict virologic failure**
- **97 patients with at least one episode of viremia >50 c/mL**
  - 25% had two or more epidsodes
- **Virologic failure (sustained viremia >200 c/mL) occurred in 9.3% of patients with “blips” and 13.9% without**
  - (RR=1.2, 95% CI 0.53, 2.64)

Havlir et al HIV Resistance Workshop, Sitges, 2000

Evolution of viremia and CD4 under prolonged HAART



Persisting in the face of failure

- Treatment benefit is a function of immune reconstitution and viral suppression
- Residual virus suppression confers residual treatment benefit
- Persistent viral replication leads ultimately to immunologic decline
- Some treatment is better than none

Strategic Treatment Interruption

Strategic treatment interruption

- Salvage therapy
- Immune stimulation

Rationale for treatment interruption in patients with drug-resistant virus

- **Wild-type virus persists in latently infected cells**
- **Drug resistant variants have reduced replicative capacity and may be less fit than wild-type**
- **In the absence of drug pressure wild-type virus re-emerges as the dominant species**
  - Devereux et al AIDS 1999;13:F123-127
  - Verhofstede et al AIDS 1999;13:2541-6

Treatment interruption

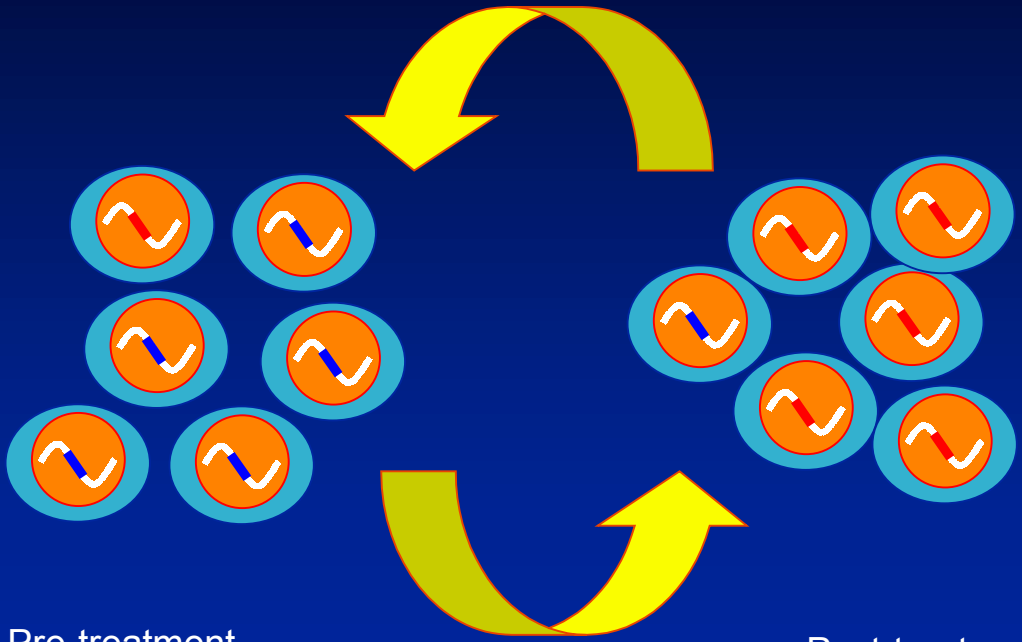
- **Plasma virus reverted to WT in 26/39 patients following treatment interruption**
- **Shift to WT virus was associated with significantly shorter time to viral suppression following resumption of therapy**
- **Treatment interruption resulted in substantial decline in CD4 cell count (-89 cells/μL)**
  - median time to recovery = 336 days

V. Miller et al 39th ICAAC 1999

STI for salvage therapy

- Is STI a successful long-term strategy for managing drug resistance, or is it just a temporizing measure?
- How long does the reservoir of drug-resistant latent virus persist in patients whose plasma virus reverts to wild-type?
- Will this reservoir lead ultimately to renewed treatment failure?

Cycling between sensitive and drug-resistant virus?

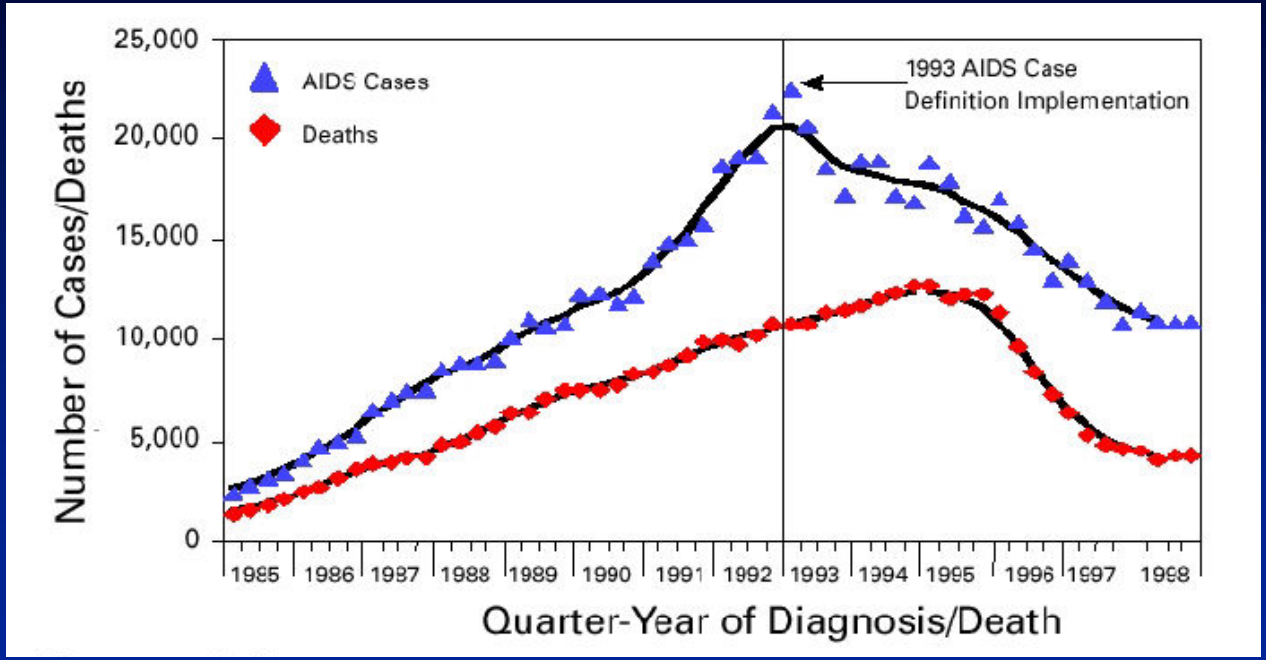


Treatment interruption and resistance

- **GENOSTOP pilot study**
  - 20 treatment-experienced patients followed for 1-6 months post treatment interruption
  - In 9/20, resistance to at least one class persisted
  - Among patients whose virus reverted to WT, resistance re-emerged in 8/11 by 3 months Calvez et al (Sitges, Abstract 141)
- **Resistant virus persists in plasma at 0.1%-1.0% of population after apparent "reversion" of dominant population to wild-type**
  - Hance et al (Sitges, Abstract 117)

Clinical implications

Estimated incidence of AIDS and AIDS-related mortality--US 1985-98*



*Persons aged ≥13 yr. Data reported through June 1999.

Conclusions

- Treatment has had a profound effect on AIDS morbidity and mortality in the developed world
- Treatment is not an emergency, but should be started after careful weighing of patient-specific factors
- When initiated, treatment should be potent, simple, and tolerable
- Switching early may remain the best strategy for first failure, but treatment benefits persist beyond virologic “failure”