

# Explanation & Update of the Federally Endorsed HIV Treatment Guidelines

-- A Provider's Perspective --

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## Overview

- Why have guidelines?
- To whom do they apply?
- Who writes them? How often are they revised and why?
- Current guidelines: how have they changed recently & why?
- What is their impact on the care of HIV+ people? Use and misuse.

## My Background

- NIH: research from federal viewpoint; public health
- Academia: the researcher's & educator's viewpoint
- FDA Division of Antiviral Drug Products Advisory Committee 1995-2000: the drug approval viewpoint
- American Academy of HIV Medicine: public policy
- Clinician: treatment issues from primary provider's perspective (ODAP/KADAP; reimbursement)

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## Why should ADAP administrators know about the guidelines?

- to understand the basis of current treatment paradigms and why drugs should be included in ADAP formularies
- to evaluate clinicians' patterns of drug use and provide a basis for quality assurance efforts
- to help negotiate with pharmaceutical companies

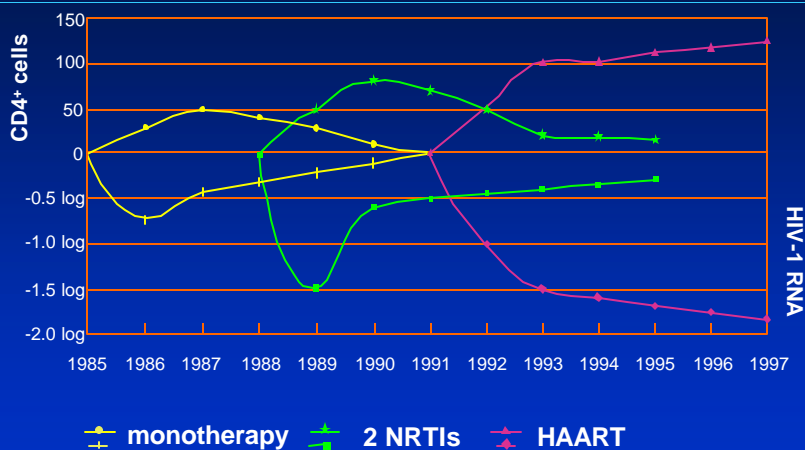
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## Goals of Antiretroviral Therapy

- to keep the patient's HIV viral load as low as possible for as long as possible
  - to decrease the viral load below the limit of detection, depending on the assay used, <400 or <50 copies/mL
- to improve the patient's immune system by increasing the CD4 cell count as high as possible for as long as possible
- and, thereby, to improve both quality of life and the duration of survival

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## Historical Perspective of Impact of Various Therapies on CD4 Cell Count & HIV Viral Load

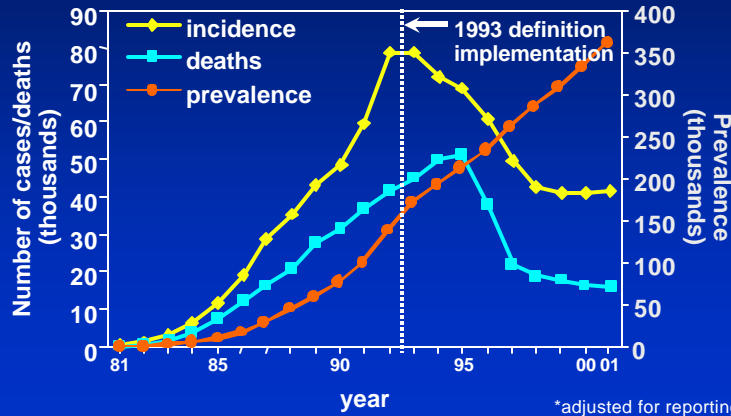


slide courtesy of CJ Cohen, MD.

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# Impact of Treatment on AIDS & Mortality

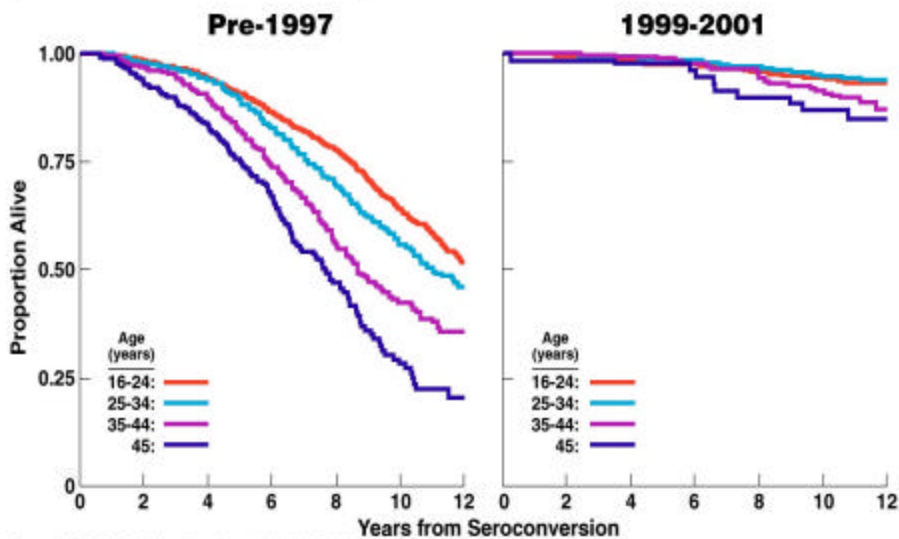
estimated incidence of AIDS, deaths, and prevalence, by year of diagnosis/death, 1981–2001



Valdiserri R, et al. 10<sup>th</sup> CROI, Boston 2003, #4; Data from the CDC

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## Risk of Progression to Death After HIV Seroconversion, Pre-1997 vs. 1999-2001



Source: CASCADE Collaboration; Lancet 362:1267, 2003.

## Why have guidelines?

- to provide data from well-designed studies ('evidence-based medicine') as guidance to clinicians...
- ...because HIV is the fastest-moving field in medicine today-- new findings are largely outdated by the time they make it through the publication cycle
- to serve as basis for adequate HIV care

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## Pace of Recent Revisions in 2003-4

- July 14, 2003
- November 10, 2003
- February 23, 2004
- another revision expected soon

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## Who writes them?

- committee of ~35 individuals involved in or concerned about HIV/AIDS care
- ~15 core members, primarily clinicians, who do most of the initial review of new data & writing
- academic, hospital & community clinics
- state & federal agencies
- patient advocacy groups

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## Who is the target audience?

- clinicians with limited HIV care experience (experienced providers say they don't need them)
- useful to HMOs, 3rd party payors, correctional facilities, Ryan White Care Act (ADAPs), because the guidelines can be used as a basis for quality assurance monitoring
- may be more helpful for medical organizations than for the individual provider

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## What criteria are used to evaluate drugs for use as initial therapy?

- guidelines are based on data from well-designed, controlled studies (“evidence-based medicine”)
- adequate study design features
  - new drug compared to current standard of care in previously untreated (“naïve”) patients
  - sufficient sample size
  - duration of at least 24 weeks and, preferably, 48
- results that demonstrate...
  - % of patients who achieve a viral load <50 & <400
  - account for the outcome of *all* patients who enrolled (“intent to treat” analysis)
  - evaluation of side effects
  - assessment of resistance development in treatment failures

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## Why have “preferred” initial regimens?

- this is a very recent change in the guidelines (2003)
- previously, guidelines used the ‘Chinese menu’ format (‘1 from Column A plus 2 from Column B’)
- now we have drugs that have proven superior in multiple comparative, randomized trials
- we have data about the durability of these potent regimens for up to 5 years
- we know more about the long-term toxicity of the other drugs used to fashion a combination regimen
- patient convenience & pill burden also considered

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# Public Health Service Treatment Guidelines for Adults & Adolescents

[www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)

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## Recommended regimens for treatment-naïve patients: U.S. Public Health Service 3/23/04

### preferred regimens

#### protease inhibitor-based

lopinavir/ritonavir +  
3TC + (ZDV or d4T)

#### non-nucleoside RTI-based

efavirenz\* +  
3TC + (ZDV or TDF or d4T)

\*EFV safety in pregnancy not established – avoid in pregnant women or women with pregnancy potential

[www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)

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## Recommended regimens for treatment-naïve patients: U.S. Public Health Service 3/23/04

### alternative regimens

| PI-based                                                 | NNRTI-based                                          |
|----------------------------------------------------------|------------------------------------------------------|
| atazanavir + (3TC or FTC) + (ZDV, d4T or ABC)            | efavirenz* + FTC + (ZDV, d4T or TDF)                 |
| fosamprenavir ± RTV + (3TC or FTC) + (ZDV or d4T or ABC) | efavirenz* + (3TC or FTC) + (ddl or ABC)             |
| indinavir + RTV + 3TC + (ZDV, d4T or ABC)                | nevirapine** + (3TC or FTC) + (ZDV, d4T, ddl or ABC) |
| lopinavir/rtv + FTC + (ZDV, d4T or ABC)                  |                                                      |
| nelfinavir + 3TC + (ZDV, d4T or ABC)                     |                                                      |
| saquinavir + RTV + 3TC + (ZDV, d4T or ABC)               |                                                      |
|                                                          | <b>Triple NRTI***</b>                                |
|                                                          | abacavir + 3TC + ZDV (or d4T)                        |

\*EFV safety in pregnancy not established – avoid in pregnant women or women with pregnancy potential

\*\*\*11% incidence of symptomatic hepatic events in women with pre-NVP CD4 cell count >250 & men with CD4 cell count >400; use with caution & monitor closely, especially during 1st 18 weeks of therapy

\*\*\*only when an NNRTI- or a PI-based regimen cannot or should not be used as first-line therapy

[www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)

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## What is new about the latest version?

- an initial regimen of 3 nucleosides has been downgraded to “alternative”
- newly-approved PIs have been added as alternatives: fosamprenavir, atazanavir
- expanded section dealing with patients who have extensive prior antiretroviral exposure

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## Are the guidelines the Holy Grail?

- No-- there have always been gray areas and limitations to our knowledge:
  - When to start?
  - How best to deal with patients who are unsuccessful with therapy?
  - What is “limited” vs “extensive” drug experience?
  - What is optimal initial therapy for patients with advanced disease (high viral load, low CD4)?
  - How to balance potency vs other treatment-related concerns? (tolerability? simplicity? salvageability?)

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## Are the guidelines the Holy Grail?

- Leeway for clinician judgment required
  - “The alternative regimens may be the preferred treatment in selected patients.”
- Fads in medicine, too
- Cost-effectiveness?

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## US Department of Health and Human Services Guidelines: When to Treat

| <i>clinical category</i>              | <i>CD4<br/>(cells/mm<sup>3</sup>)</i> | <i>viral load<br/>(copies/mL)</i> | <i>recommendation</i>                                      |
|---------------------------------------|---------------------------------------|-----------------------------------|------------------------------------------------------------|
| symptomatic (AIDS or severe symptoms) | any                                   | any                               | treat                                                      |
| asymptomatic                          | <200                                  | any                               | treat                                                      |
| asymptomatic                          | >200-350                              | any                               | offer treatment;<br>controversy exists                     |
| asymptomatic                          | >350                                  | >30K (bDNA)<br>>55K (RT-PCR)      | opinions differ;<br>some treat (3 yr risk of<br>AIDS >30%) |
| asymptomatic                          | >350                                  | <30K (bDNA)<br><55K (RT-PCR)      | most defer therapy<br>(3 yr risk of AIDS <15%)             |

Table 4 from [www.aidsinfo.nih.gov/guidelines/adult](http://www.aidsinfo.nih.gov/guidelines/adult) 3/23/04

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## WHO Guidelines for Antiretroviral Therapy in the Developing World

- When to start
  - symptomatic disease or CD4 <200 cells (if CD4 count available)
- What to start
  - Combivir® (AZT+3TC) + EFZ or NVP [2 NRTIs + 1 NNRTI]
  - Trizivir® (AZT+3TC+ABC) [3 NRTIs]
  - Combivir® + indinavir/r \* or lopinavir/r or saquinavir/r or nelfinavir [2 NRTIs + 1 PI]
- How to monitor TX (min. lab requirements)
  - required: HIV antibody, hemoglobin
  - basic: wbc differential, ALT or AST, creatinine or BUN, glucose, pregnancy test
  - desirable: CD4 cell count, bilirubin, amylase, lipids
  - optional: HIV RNA

\* “/r” indicates combination with low-dose ritonavir (“boosting”)

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# Antiretroviral Drugs: Challenges and Needs

## Challenges

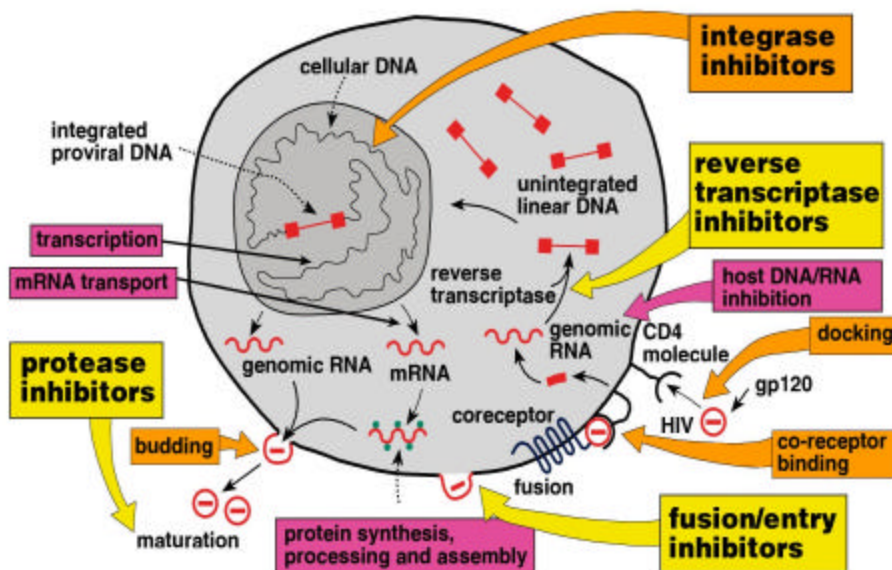
- Adherence
- Toxicity
- Activity
- Resistance

## Needs

- Improve convenience
- Improve tolerability
- Improve pharmacokinetics
- Reduce toxicity
- Improve activity against...
  - wild-type virus
  - resistant virus
- Penetrate reservoirs (brain, genital tract)
- Exploit new targets

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## Targets for Antiretroviral Drugs



## Why are they revised so often?

- keep pace with new data about older drugs and specific combinations
- remain up-to-date with the pace of new drug development
- refine knowledge about drug interactions
- outwit resistance
- reflect changing attitudes in practitioner & patient communities

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## When to start therapy?

eradication = goal

virologic suppression

immunologic control

decreased transmission

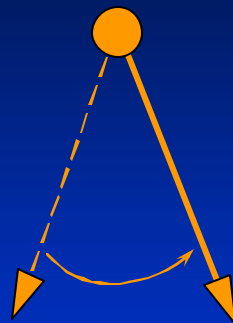
eradication not possible

decreased quality-of-life

long-term toxicity

resistance

benefit of HAART at lower CD4 counts

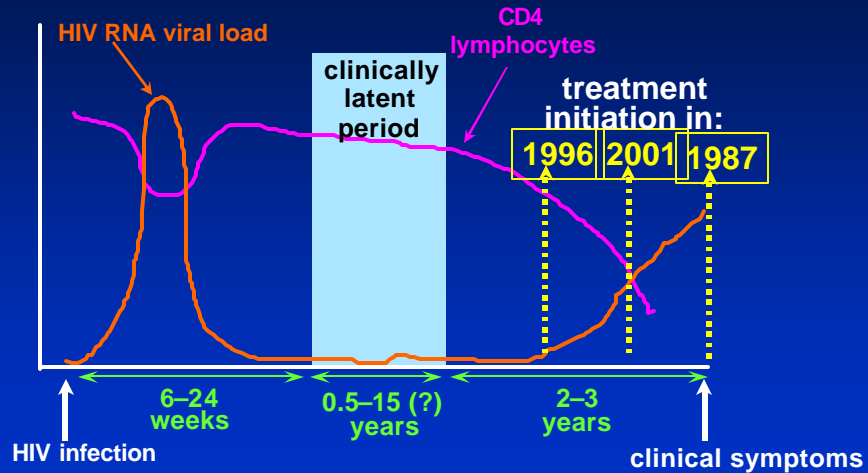


- 'Hit early, hit hard'
- start TX based on viral load

- defer therapy, then 'hit hard'
- start TX based on CD4 count

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# When to start therapy?



both CD4 counts and viral load considered since 2001

# “Buffalo hump”



BEFORE

AFTER

RELAPSE

- some adverse effects of ART include dramatic changes in body shape
- “lipodystrophy”, “lipoatrophy”

# Importance of patient adherence

poor adherence

↘ resistance

↘ drug failure

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## Tradeoffs: balancing potency vs other treatment-related concerns

- What is optimal therapy for pts with advanced disease (high viral load, low CD4)? For pts with moderate disease?
- How to balance potency vs tolerability? simplicity? salvageability?
- Is simpler always better?
  - DMP 006: EFZ (3 caps at bedtime/no food restrictions) better than IDV (2 caps q8h on empty stomach) for pts with VL>100K
  - ACTG 5095: Trizivir® (AZT/3TC/Abacavir in 1 tab BID) inferior to Combivir® (AZT/3TC in 1 tab BID)/EFZ and Trizivir®/EFZ regardless of VL

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## Current status of antiretrovirals in 2004

- there are 20 approved individual drugs
  - 2 (ddC, delavirdine) are used infrequently
  - 1 (ritonavir) is primarily used as a pharmacokinetic booster to ↓ # of pills and ↑ interval between dose of other drugs [??impact of recent Norvir price ↑]
- ***no antiretroviral drug is ideal***
  - short- and long-term side effects
  - too many pills and/or dietary requirements
  - differences in potency
  - some have low threshold for development of resistance

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## Resistance Development Drives New Drug Discovery

- current FDA-approved drugs fall into 4 classes
- within each class the agents are chemically similar, so that resistance to one often confers resistance to others in the same class (“cross-resistance”)...
- ...and cross-resistance to these similar structures limits treatment options in patients with resistant virus
- development of new agents and strategies to overcome problems with existing drugs is of paramount importance to patients & treaters

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## How should the guidelines best be used?

- **guidelines** serve as a **baseline or threshold** for adequate HIV care
- **adequate** care is not the same thing as **optimal** care
- they **cannot** and **should not** be used to create a restrictive formulary
- resistance development and patient-specific circumstances must be taken into consideration to deliver optimal care to **every** HIV+ person

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## Use exaMPLES....ow should they be used?

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## Factors that influence therapeutic success

### % with undetectable viral load

0%

100%

late disease

early disease

antiretroviral-experienced

antiretroviral-naive

low-potency regimen

high-potency regimen

highly toxic regimen

minimally toxic regimen

lack of patient education

well-informed patient

slide courtesy of J. Schapiro, MD.

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## Limitations of Current Therapy

- Eradication not possible with current ART\*
  - dormant virus in resting memory CD4 T cells → latent reservoirs
  - replication continues despite undetectable viremia
    - virions with half-life of 30 min
    - CD4s with half-life of <1 day
    - 250 generations per year, if untreated
- Short- and long-term adverse effects
  - fatigue, headache, nausea, diarrhea, abd. discomfort, anemia, CNS side effects, rash
  - peripheral neuropathy, pancreatitis, hepatic dysfunction, hyperlipidemia, ⚠ cardiovascular risk, diabetes, lipodystrophy

\*Ho D. PL-1, First IAS Conference on HIV Pathogenesis and Treatment, July 8 – 11, 2001.

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## Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- zidovudine (AZT, ZDV, Retrovir ®)
- didanosine (ddI, Videx ®)
- zalcitabine (ddC, Hivid ®)
- stavudine (d4T, Zerit ®)
- lamivudine (3TC, Epivir ®)
- abacavir (ABC, Ziagen ®)
- AZT + 3TC (Combivir ®)
- AZT + 3TC + ABC (Trizivir ®)
- tenofovir (TDF, Viread ®)\*
- emtricitabine (FTC, Emtriva® )

\*nucleotide RTI

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## Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- nevirapine (NVP, Viramune ®)
- delavirdine (DLV, Rescriptor ®)
- efavirenz (EFZ, Sustiva ®)

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## Protease Inhibitors (PIs)

- saquinavir (SQV, Invirase ®, Fortovase ®)
- indinavir (IDV, Crixivan ®)
- ritonavir (RTV, Norvir ®)
- nelfinavir (NFV, Viracept ®)
- amprenavir (APV, Agenerase ®)
- lopinavir + ritonavir (LPV/r, Kaletra ®)
- atazanavir (TAZ, Reyataz®)
- fosamprenavir (FAPV, Lexiva®)

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## Fusion Inhibitors (FIs)

- Enfuvirtide (T-20, Fuzeon ®)

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## Defining Highly Active Antiretroviral Therapy (HAART)

- initially consisted of 2 NRTIs + 1 PI
- with development of potent NNRTIs (especially efavirenz), also came to include 2NRTIs + 1 NNRTI
- subsequent combinations less fully tested, so it is not clear that they will confer equal benefit:
  - 2 PIs
  - 1 PI + 1 NNRTI
  - 3 NRTIs
  - FI + 2 other agents

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## Why Does HIV Resistance Occur?

- patient nonadherence
- suboptimal dosing of drugs
- spontaneous mutation of the HIV genome
- transmission of drug-resistant virus

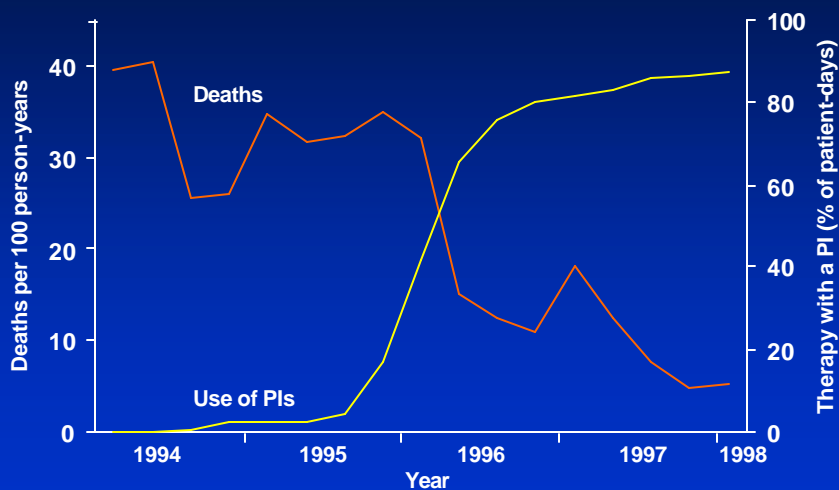
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## Anti-HIV agents in clinical trials

- Docking
- Co-receptor binding
- Fusion inhibitors
- Host DNA/RNA editing
- RT inhibitors
- Integrase Inhibitors
- Transcription
- Protein synthesis and assembly
- mRNA transport
- Budding
- Maturation (PI's)

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## AIDS mortality and protease inhibitor (PI) use



Palella et al. N Engl J Med 1998

## Adherence and Clinical Outcome

- while meticulous adherence to ART is considered essential, the parameters of adherence that lead to optimal outcomes have not yet been defined experimentally
- how adherent must one be to succeed?
- even in clinical trials (optimal setting), 15-35% do not achieve/maintain undetectable VL
- not all treatment failure is failure of adherence
  - impaired drug absorption/metabolism
  - intolerance
  - history of serial monotherapy leading to resistance
  - de novo acquisition of resistant HIV

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## Factors Influencing Therapeutic Success

| % with undetectable viral load |                         |
|--------------------------------|-------------------------|
| 0%                             | 100%                    |
| Late (advanced) disease        | Early disease           |
| Antiretroviral experienced     | Antiretroviral naive    |
| Low-potency regimen            | High-potency regimen    |
| Highly toxic regimen           | Minimally toxic regimen |
| Lack of patient education      | Patient education       |

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## Importance of Patient Adherence

### Poor Adherence

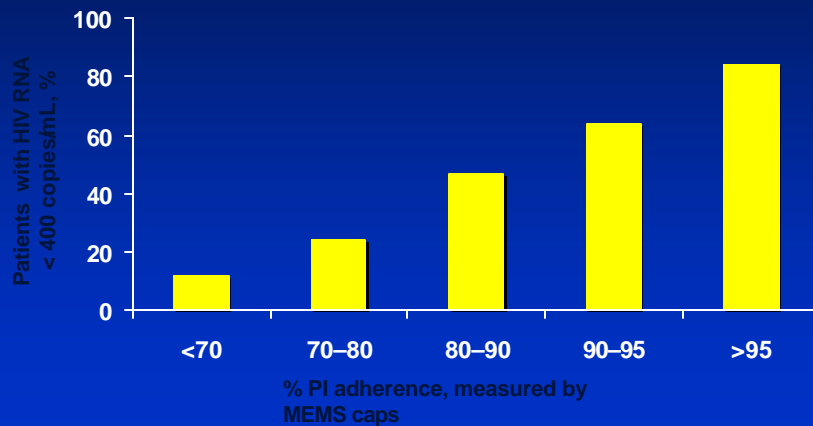
↪ Resistance

↪ Drug Failure

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## What Degree of Adherence is Needed?

adherence to a PI-containing regimen correlates with HIV RNA response at 3 months



Paterson DL et al. *Ann Intern Med* 2000;133:21-30.

## What Is HIV Drug Resistance?

- **Phenotypic resistance** - the ability of HIV to grow in high drug levels
  - usually reported as the fold increase in  $IC_{50}$  relative to a sensitive reference virus
- **Genotypic changes** - viral mutations that cause resistance
  - reported as changes in the amino acid sequence relative to wild-type

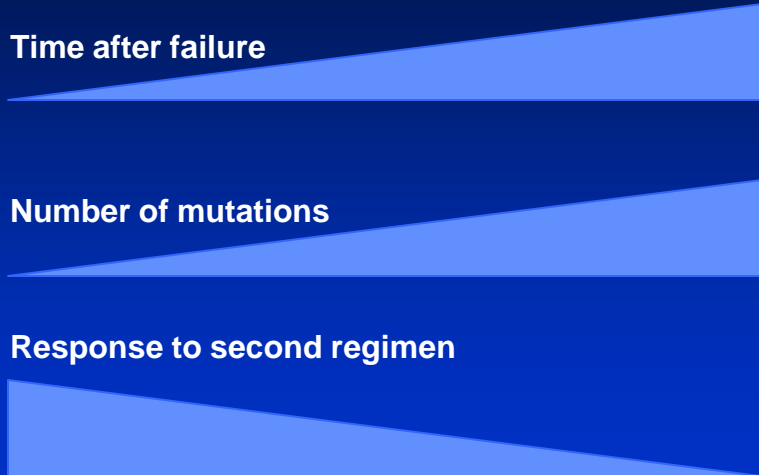
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## What are Some of the Signs of Treatment Failure/Resistance?

- viral Load (VL) increase
- CD4 cell count decrease
- development of opportunistic infections
- other clinical signs and symptoms of uncontrolled viral replication, such as weight loss, fever, fatigue

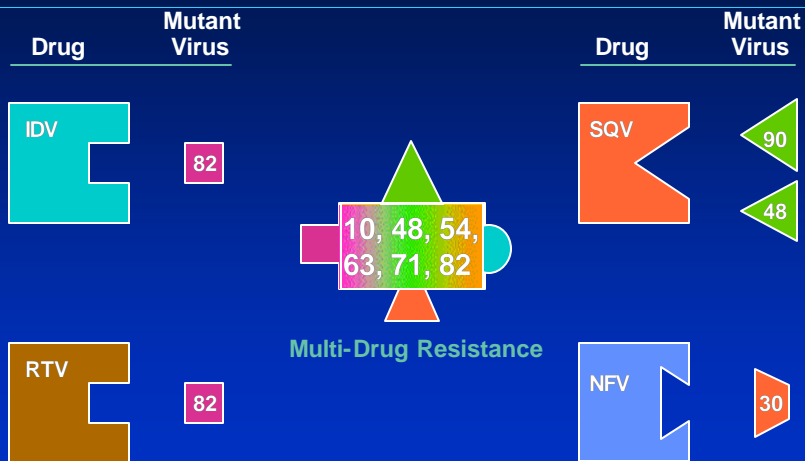
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# Resistance Accumulation



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# Accumulation of Mutations May Result in Broad Cross-Resistance



Source: Shafer et al. In: Abstracts of International Workshop on HIV Drug Resistance, Treatment Strategies and Eradication; June 25-28, 1997; St Petersburg, Fla.

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# HIV life cycle and potential targets for therapy

