Managing HIV: Current Guidelines

Judith Feinberg, MD

Professor of Medicine
University of Cincinnati College of Medicine
Cincinnati, Ohio

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IAS-USA Guidelines

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What the Guidelines Address

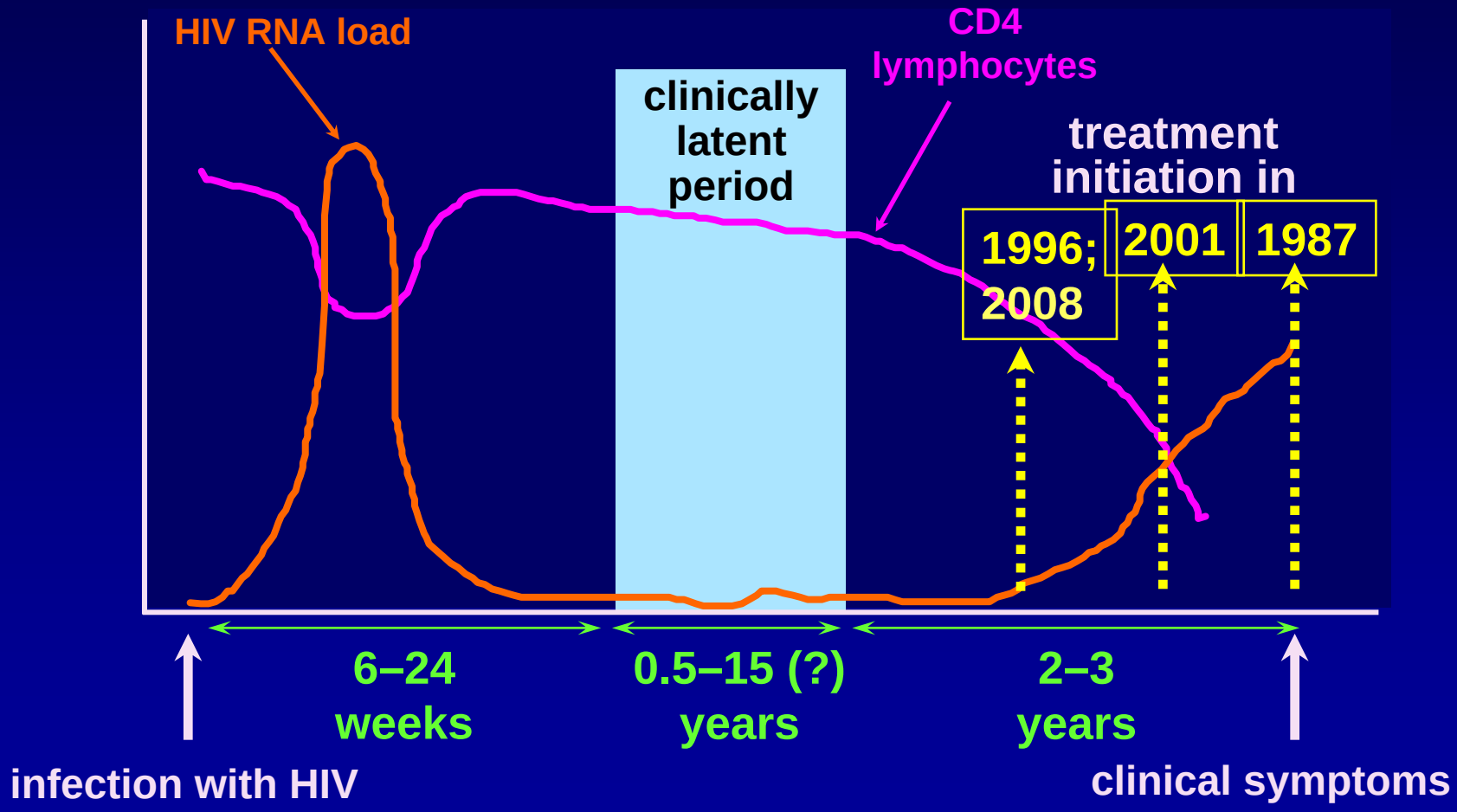
- Baseline evaluation
- Laboratory testing (HIV RNA, CD4 cell count, resistance)
- When to initiate therapy
- When to change therapy
- Therapeutic options
- Adherence
- ART-associated adverse effects

What the Guidelines Address (*cont*)

- Treatment of acute HIV infection
- Special considerations in:
  - Adolescents
  - Pregnant women
  - Injection drug users
  - Coinfection with HBV, HCV, or TB
- Prevention counseling for HIV-infected patients

When to Start

When to Start Therapy?



- Beginning in 2001, both CD4 counts and VL considered

Use of CD4 Cell Counts to Guide Therapy Decisions

- CD4 count
  - Major indicator of immune function
  - Most recent CD4 count is best predictor of disease progression
  - CD4 count usually is the important consideration in decision to start ART
  - Important in determining response to ART
  - Adequate response: CD4 increase 100–150 cells/μL per year
- Interval CD4 monitoring
  - Check at baseline (×2) and at least every 3-6 months

Use of HIV RNA Levels to Guide Therapy Decisions

- HIV RNA ("viral load")
  - Less important than CD4 count, but may influence decision to start ART and help determine frequency of CD4 monitoring
  - Critical in determining response to ART
  - Goal of ART: HIV RNA below limit of detection (<40 to <80 copies/mL, depending on assay)
- Interval HIV RNA monitoring
  - Check at baseline (×2) and at least every 3-4 months with stable patients
  - Immediately before initiating ART
  - 2-8 weeks after start or change of ART to assess response

Potential Benefits of Early Therapy
(CD4 count >350 cells/μL)

- Potent ART may improve and preserve immune function in most patients with virologic suppression, regardless of baseline CD4 count
  - Maintain higher CD4 count
  - Prevent irreversible immune system damage
  - Decrease risk of HIV-associated complications
    - e.g., TB, NHL, KS, peripheral neuropathy, HPV-associated malignancies, HIV-associated cognitive impairment
  - deCrease risk of nonopportunistic conditions and non-AIDS-associated conditions
    - e.g., CV, renal, and liver disease; malignancies; infections
  - Decrease risk of HIV transmission

Indications for Initiating ART: Chronic Infection

Clinical Category or CD4 Count	Recommendation
• History of AIDS-defining illness • CD4 count <350 cells/μL (IAS 8/08: treat) • Pregnancy • HIV-associated nephropathy • Hepatitis B coinfection, when HBV treatment is indicated*	Initiate ART

*Treatment with fully suppressive drugs active against both HIV and HBV is recommended.

*Note: OI Guidelines (x, 08) recommends …….

Indications for Initiating ART: Chronic Infection (*cont*)

Clinical Category or CD4 Count	Recommendations
• CD4 >350 cells/µL, asymptomatic, without conditions listed above	• Optimal time to initiate ART is not well defined • Consider individual patient characteristics and comorbidities • (IAS 8/08: consider TX)

*Treatment with fully suppressive drugs active against both HIV and HBV is recommended.

*Note: OI Guidelines (x, 08) recommends …….

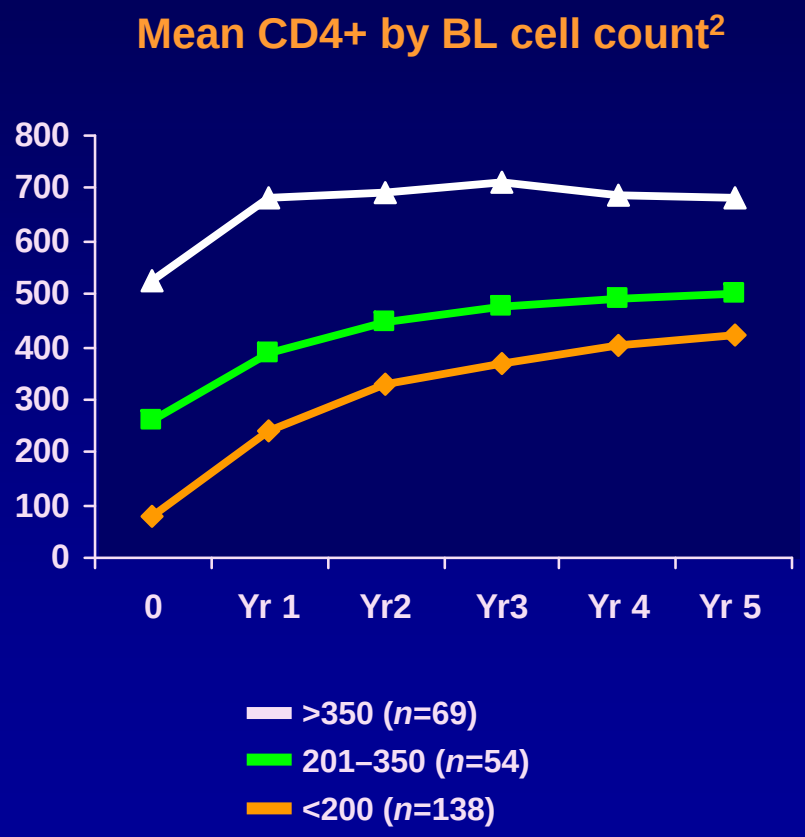
New Data on Earlier Initiation of Therapy

- Rates of AIDS-defining illnesses lower when Highly Active Antiretroviral Therapy (HAART) started at higher CD4 counts[1]
  - Patients starting with <200 vs 201-350 cells/µL
    HR 3.30 (95% CI: 2.51, 4.33)
  - Patients starting with 201-350 vs 351-500 cells/µL
    HR 1.46 (95% CI: 0.96, 2.21)
- After 5 yrs, pts who started HAART with lower CD4 counts never achieve levels comparable to those who initiate HAART with CD4 >350 cells/µL[2]
- HOPS database: starting TX at higher CD4 cell counts results in better outcomes[3]
  - Reduced incidence of mortality and OIs
  - Both CD4 cell count and viral load responses improved

[1.] Sterne J, et al. 13th CROI, 2006, #525. [2.] Keruly JC, et al. 13th CROI, 2006, #529. [3.] Lichtenstein KA, et al. 13th CROI, 2006, #769.

Long-term CD4+ Response to ART Based on CD4 Cell Count at Initiation

- **JHU HIV clinical cohort (5 yr follow-up)**
  - ≥1 year follow-up after initiation of ART
  - Persistent HIV RNA <400 c/mL during ART
  - Multivariate analysis of risk for reduced CD4+ response:
    - IDU
    - However, gender, race, type of ART are NOT associated with CD4+ change

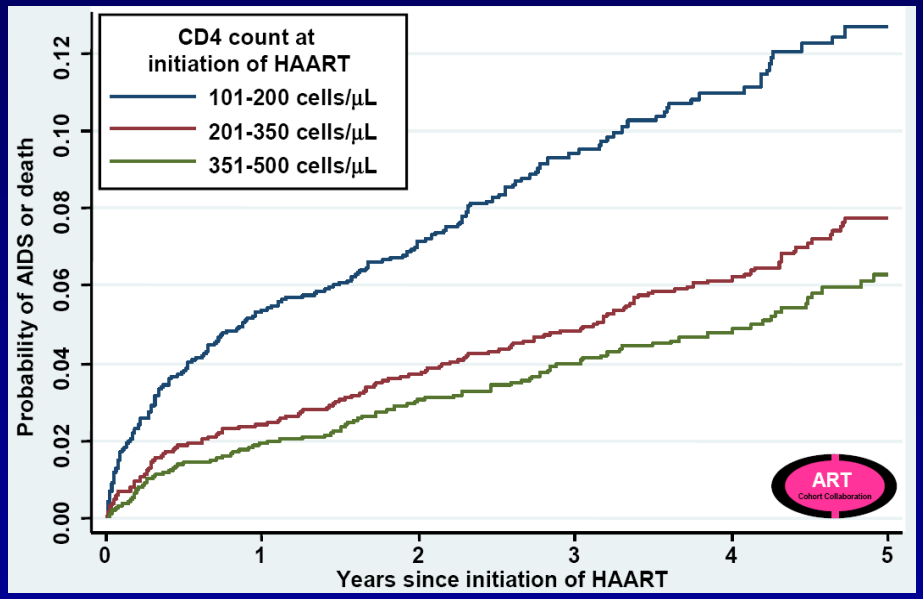


Keruly J . 13th CROI, Denver, Feb 2006, #529.

Clinical Outcomes Related to CD4 Cell Count at Initiation of ART

- Timing of initiation of ART in naïve subjects (*n*=10,885) in the ART Cohort Collaboration (ART-CC)
  - Median follow-up 2.7 years
- Hazard ratio for progression to AIDS or death by CD4+ cells at initiation of ART:
  - ≤200 vs 201–350
    HR 2.93 (95% CI: 2.41, 3.57)
  - 201–350 vs 351–50
    HR 1.26 (95% CI: 0.94, 1.68)
- Trend favoring outcomes for ART initiation at >350 CD4+ cells

Cumulative Probability of AIDS/ Death According to CD4+ Count at Initiation of HAART



Sterne J, et al. 13th CROI, Denver 2006, #525 (courtesy of ART Cohort Collaboration).

What to Use and Why

“Preferred” vs “Alternative” Regimens

- Preferred regimens:
  - Clinical trials data suggest optimal efficacy and durability with acceptable tolerability and ease of use
- Alternative regimens
  - Clinical trials data show efficacy, but it is considered alternative due to disadvantages compared to the preferred regimens in terms of
    - Antiviral activity,
    - Demonstrated durable effect,
    - Tolerability, or
    - Ease of use

http://aidsinfo.nih.gov/guidelines/

Components of Initial ART: DHHS Categories

- Preferred
  - Clinical data show optimal efficacy and durability
  - Acceptable tolerability and ease of use
- Alternative
  - Clinical trial data show efficacy but also show disadvantages in ARV activity, durability, tolerability, or ease of use (compared with “preferred” components)
  - May be best option in select individual patients
- Other options
  - Inferior efficacy or greater or more serious toxicities

Initial Treatment: Preferred Components

NNRTI option

- EFV*

OR

PI options

- ATV + RTV
- FPV + RTV (BID)
- LPV/RTV (BID)

+

NRTI options[1]

- ABC + 3TC[2]
- TDF + FTC[3]

* Avoid in pregnant women and women with pregnancy potential.
[1]FTC can be used in place of 3TC and vice versa.
[2]For patients who have tested negative for HLA-B*5701.
[3]TDF + FTC or 3TC is preferred for patients with HIV/HBV coinfection.

Initial Treatment: Alternative Components

NNRTI option

- **NVP***

PI options

- **ATV[1]**
- **FPV**
- **FPV + RTV (once daily)**
- **LPV/RTV (once daily)[2]**
- **SQV + RTV**

*NVP should not be initiated in women with CD4 counts of >250 cells/µL or men with CD4 counts of >400 cells/µL.

[1]ATV must be boosted with RTV if used with TNF.

[2]May be insufficient if HIV RNA >100,000 copies/mL.

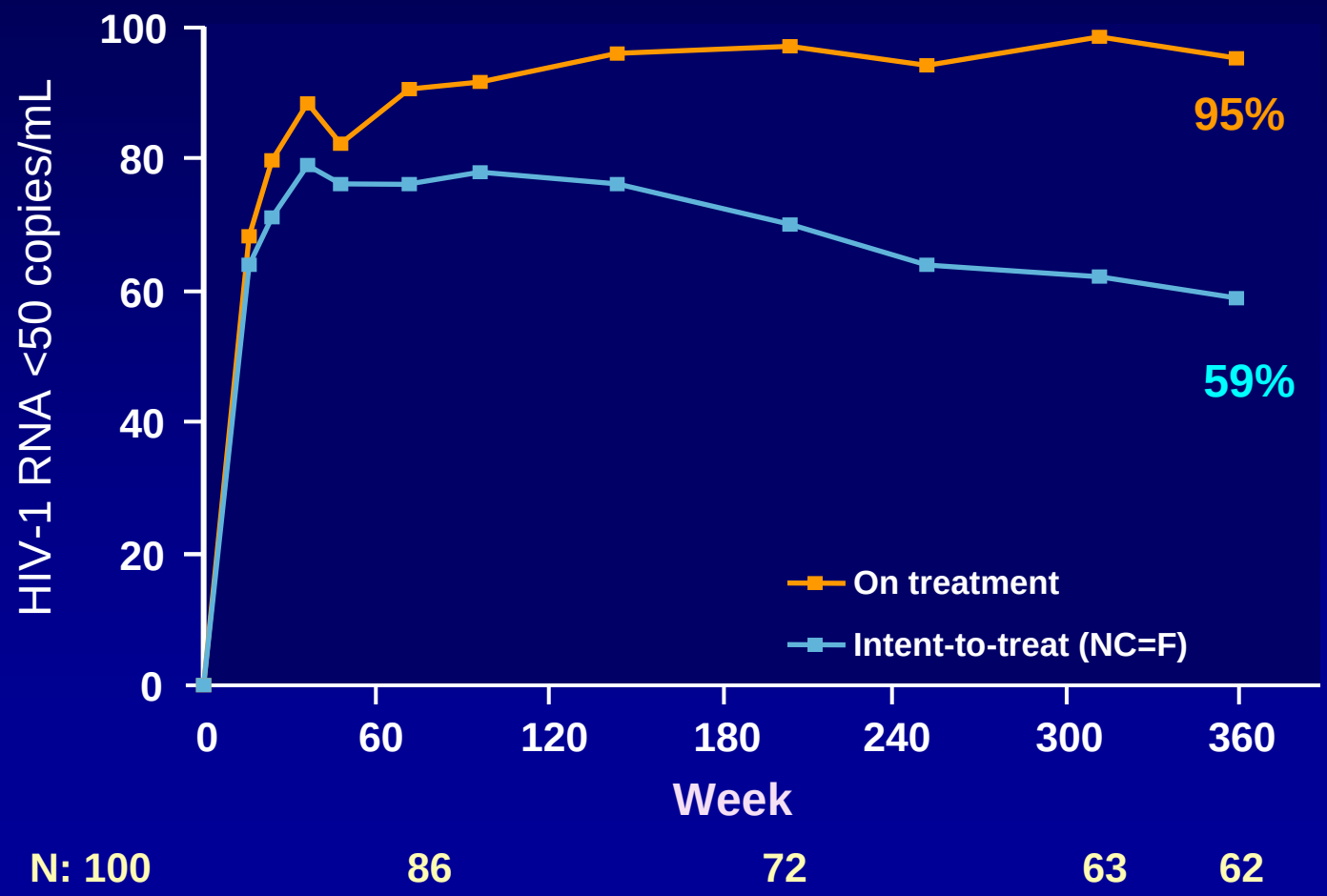
Initial Treatment: Alternative Components (*cont*)

NRTI Options
(in order of preference)

- **ZDV + 3TC***
- **ddI + (FTC or 3TC)**

*FTC can be used in place of 3TC and vice versa.

Virologic Response in Naïve Patients HIV-1 RNA <50 copies/mL through 7 Years

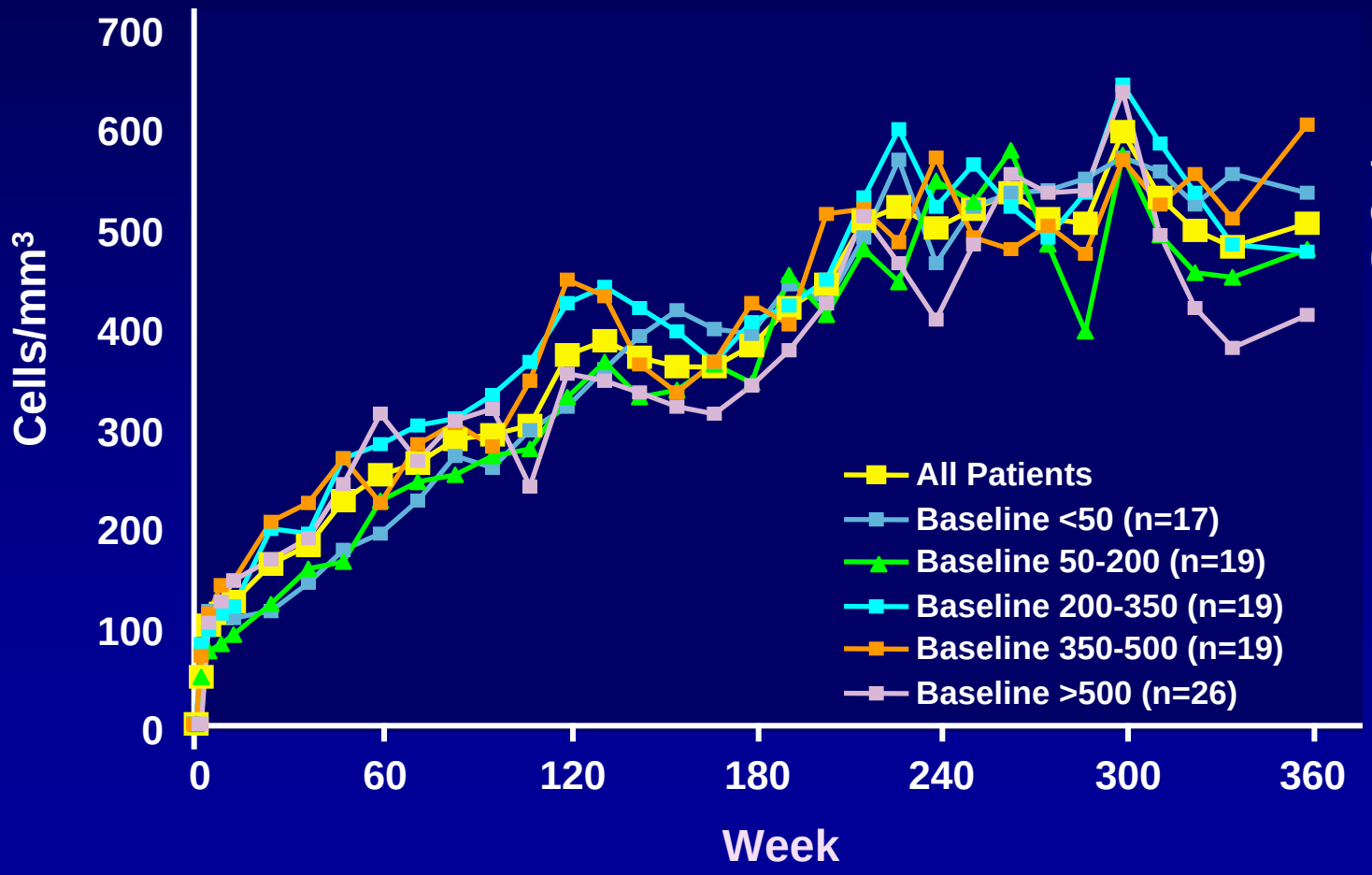


Murphy R, et al. 10th EACS, Dublin, Ireland, November 2005, #P7.9/3.

Study 720

Mean Change in CD4 Count Through 7 Years

Mean Absolute Value at Year 7 = 776 Cells/mm^3



Murphy R, et al. 10th EACS, Dublin, Ireland, November 2005, #P7.9/3.

Study 720

Current Antiretroviral Medications 2008

- **NRTI**
  - Abacavir — ABC
  - didanosine — ddI
  - emtricitabine — FTC
  - Lamivudine — 3TC
  - Stavudine — d4T
  - Tenofovir — TDF
  - (zalcitabine — ddC)
  - Zidovudine — ZDV, AZT
- **NNRTI**
  - Delavirdine — DLV
  - Efavirenz — EFV
  - Nevirapine — NVP
  - Etravirine — ETR
- **Fusion Inhibitor**
  - Enfuvirtide — T-20
- **PI**
  - Atazanavir — ATV
  - Darunavir — DRV
  - Fosamprenavir — FPV
  - Indinavir — IDV
  - lopinavir/r — LPV
  - Nelfinavir — NFV
  - Ritonavir — RTV
  - Saquinavir — SQV
  - Tipranavir — TPV
- **CCR5 Inhibitor**
  - Maraviroc — MRV, MRC
- **Integrase Inhibitor**
  - Raltegravir — RAL

Antiretrovirals on the Horizon 2008-9

- R5 coreceptor inhibitors
  - Vivriviroc VCV
- NNRTI
  - Rilpivirine (TMC-278) RIL
- Integrase inhibitors
  - Elvitegravir (GS 9137) ELV

Patient Monitoring

- Activity
- Tolerability/Specific adverse effect profile
- Ease of administration
- Adherence
- Genetic barrier to resistance
- Cross-resistance
- Presence of chronic hepatitis B/C coinfection
- Other comorbid conditions/risks (e.g., diabetes, heart disease)
- Patient preference
- IAS 8-08: monitor frequently initially (e.g., 2, 4, 8 wks and every 4 wks thereafter until VL <50; then every 3-4 months)

http://aidsinfo.nih.gov/guidelines/

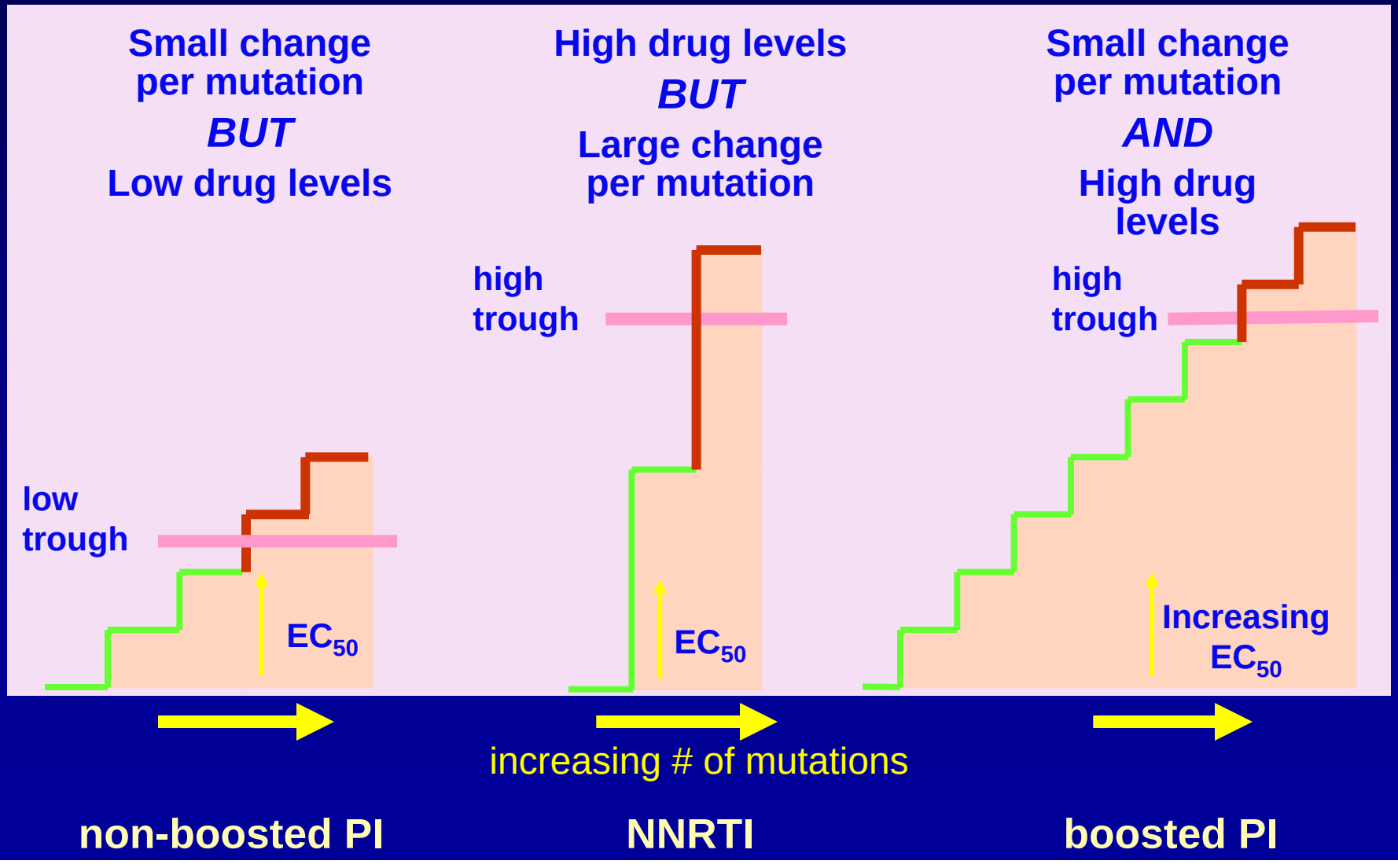
Factors to Consider in the Choice of Antiretroviral Therapy

Choosing a Specific Regimen

- Activity
- Tolerability/specific adverse effect profile
- Ease of administration
- Adherence
- Genetic barrier to resistance
- Cross-resistance
- Presence of chronic hepatitis B/C coinfection
- Other comorbid conditions/risks (e.g., diabetes, heart disease)
- Patient preference

http://aidsinfo.nih.gov/guidelines/

Pharmacokinetic and Genetic Barriers to Resistance



Chronic Viral Hepatitis Co-infection

- Majority of deaths in HAART era now not AIDS-associated; ESLD is primary cause in several studies[1-3]
- Hepatitis B
  - Complicated by the overlapping spectrum of HIV drugs for HBV
  - Hep B flares when HIV drugs with HBV activity are stopped
  - Availability of drugs for HB with NO HIV activity (e.g. adefovir, telbivudine, interferon) makes treatment of HBV alone plausible
  - Entecavir
- Hepatitis C
  - Bilateral interaction of HCV/HIV on disease progression
  - Antihcv therapy is costly and raises tolerability issues
  - Availability of tenofovir lessens anemia associated with AZT use

1. Palella FJ, et al. *JAIDS*. 2006;43:27-34; 2. D:A:D Study. *Arch Intern Med*. 2006;166:1632-41;
3. Crum NF, et al. *JAIDS*. 2006;41:194-200.

Role of Resistance Testing

Testing for Drug Resistance

- Before initiation of ART:
  - Resistance testing (genotype) recommended for all at entry to care
  - Recommended for all pregnant women
  - Transmitted resistance in 6-16% of HIV-infected patients
  - Identification of resistance mutations may optimize treatment outcomes
  - In absence of therapy, resistance mutations may decline over time and become undetectable by current assays, but may persist and cause treatment failure when ART is started
- Patients with virologic failure:
  - Perform while patient is taking ART, or ≤4 weeks after discontinuing therapy
  - Interpret in combination with history of ARV exposure and ARV adherence

Use of Drug Resistance Testing

Recommended	Comment
Acute HIV infection, if treatment is to be started	▪ To determine if resistant virus was transmitted; guide treatment decisions ▪ Consider resistance testing if treatment is deferred
Chronic HIV infection before starting ART	▪ Transmitted drug-resistant virus is common in some areas; is more likely to be detected earlier in the course of HIV infection; consider resistance testing earlier in the course of infection
Pregnancy	▪ Recommended before initiation of ART or prophylaxis, or if incomplete viral suppression on ART
Virologic failure during ART	▪ To assist in selecting active drugs for a new regimen
Suboptimal suppression of VL after starting ART	▪ To guide treatment decisions

Other Assessment and Monitoring Studies

- HLA-B*5701 screening
  - Recommended before starting abacavir, to reduce risk of hypersensitivity reaction (HSR)
  - HLA-B*5701-positive patients should not receive ABC
  - Positive status should be recorded as an ABC allergy
  - If HLA-B*5701 testing is not available, ABC may be initiated after counseling and with appropriate monitoring for HSR
- Coreceptor tropism assay
  - Should be performed when a CCR5 antagonistis being considered
  - Consider in patients with virologic failure on a CCR5 antagonist

When to Stop

When to Stop: Ideally, Never

- Structured Treatment Interruptions (STIs): multiple recent studies show no beneficial effect, and sometimes clinical deterioration, by using STIs as a treatment strategy
- Because MDR-HIV often has diminished replication efficiency, at a minimum maintaining a failing regimen exerts continued selection pressure for a less-fit virus
- In patients with multiple regimen failure, if at least 2 new active agents cannot be identified, strong consideration should be given to maintaining the current regimen until new drugs become available, assuming clinical and immunological stability

http://aidsinfo.niv.gov/guidelines/

About Guidelines…

- It is important to remember that guidelines are recommendations, not rules
- Above all, HIV therapy needs to be individualized
  - An alternative regimen may be preferred for some patients
  - A preferred regimen may not be appropriate for all patients
- It is advisable to avoid the combinations that the guidelines recommend against using