Progress in Anti-retroviral Therapy

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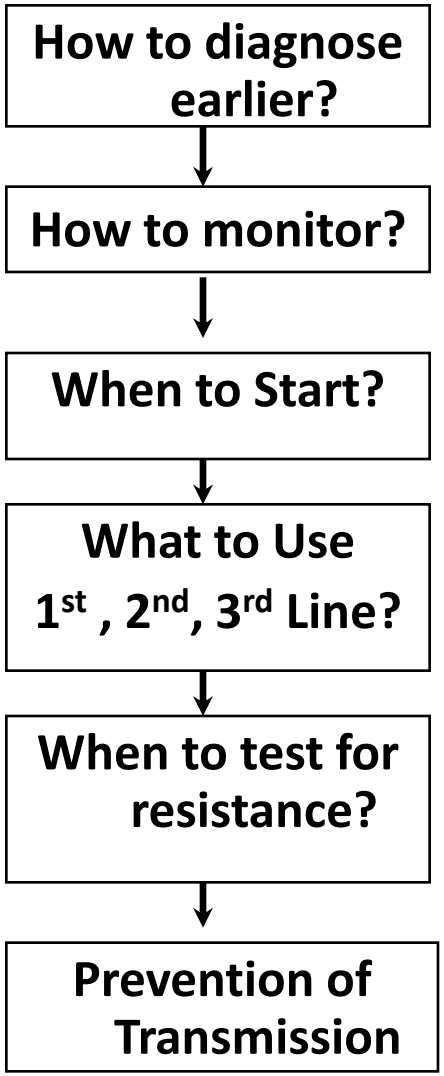
ART treatment Issues

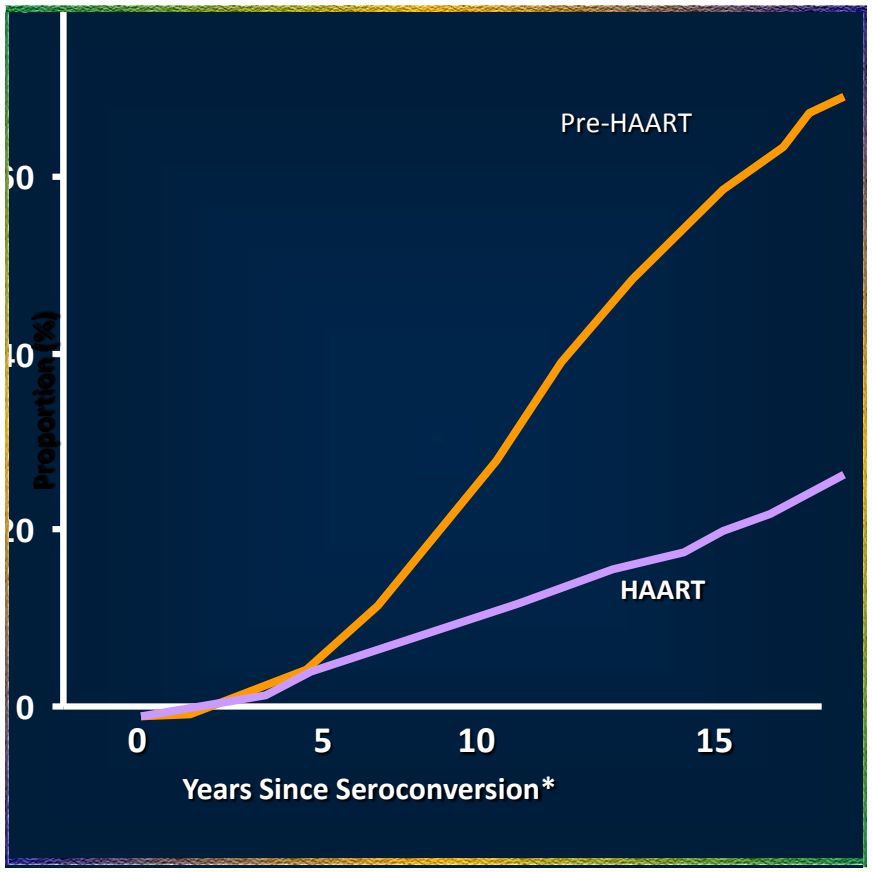


Critical patient & public health important outcomes:

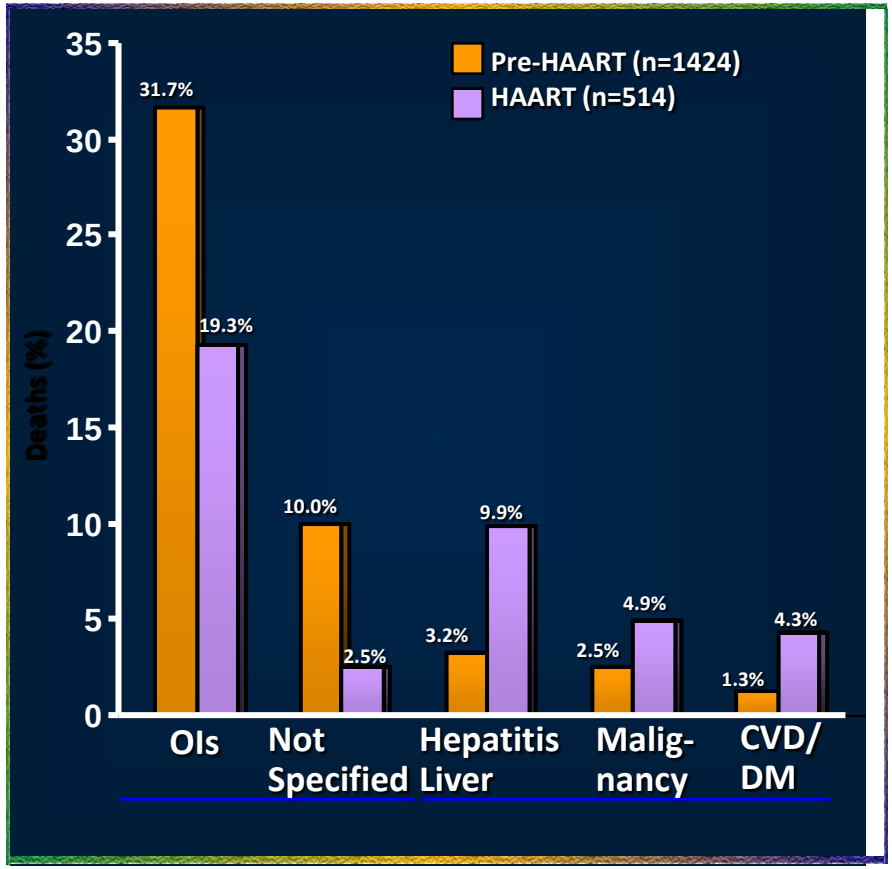
- **Mortality**
- **Disease progression (morbidity)**
- **Severe or regimen limiting adverse events**
- **Adherence & retention on ART**
- **Durability of regimen effect**
- **Reduction of HIV transmission**
- **Cost**

Overall Mortality and Causes of Death

Overall Mortality*



Causes of Death†



*n=7680 seroconverters, of whom 1938 died (26%; 1424 pre-HAART and 514 during HAART).

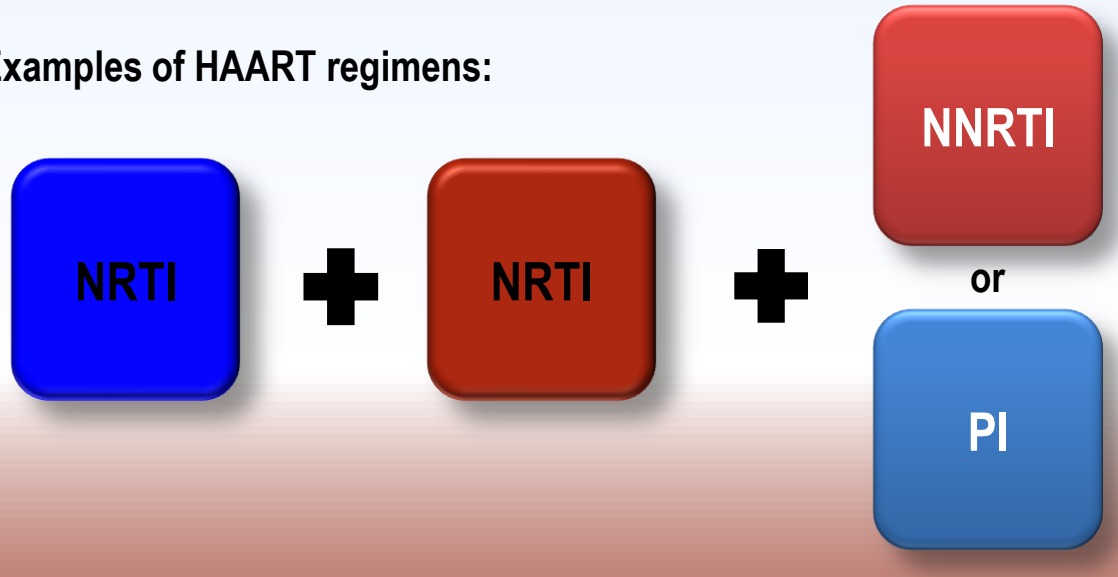
†no change in the following causes of death: AIDS-related malignancy, other infections, organ failure, and unknown causes.

Smit C, et al. *AIDS.* 2006;20:741-749.

What Is HAART?

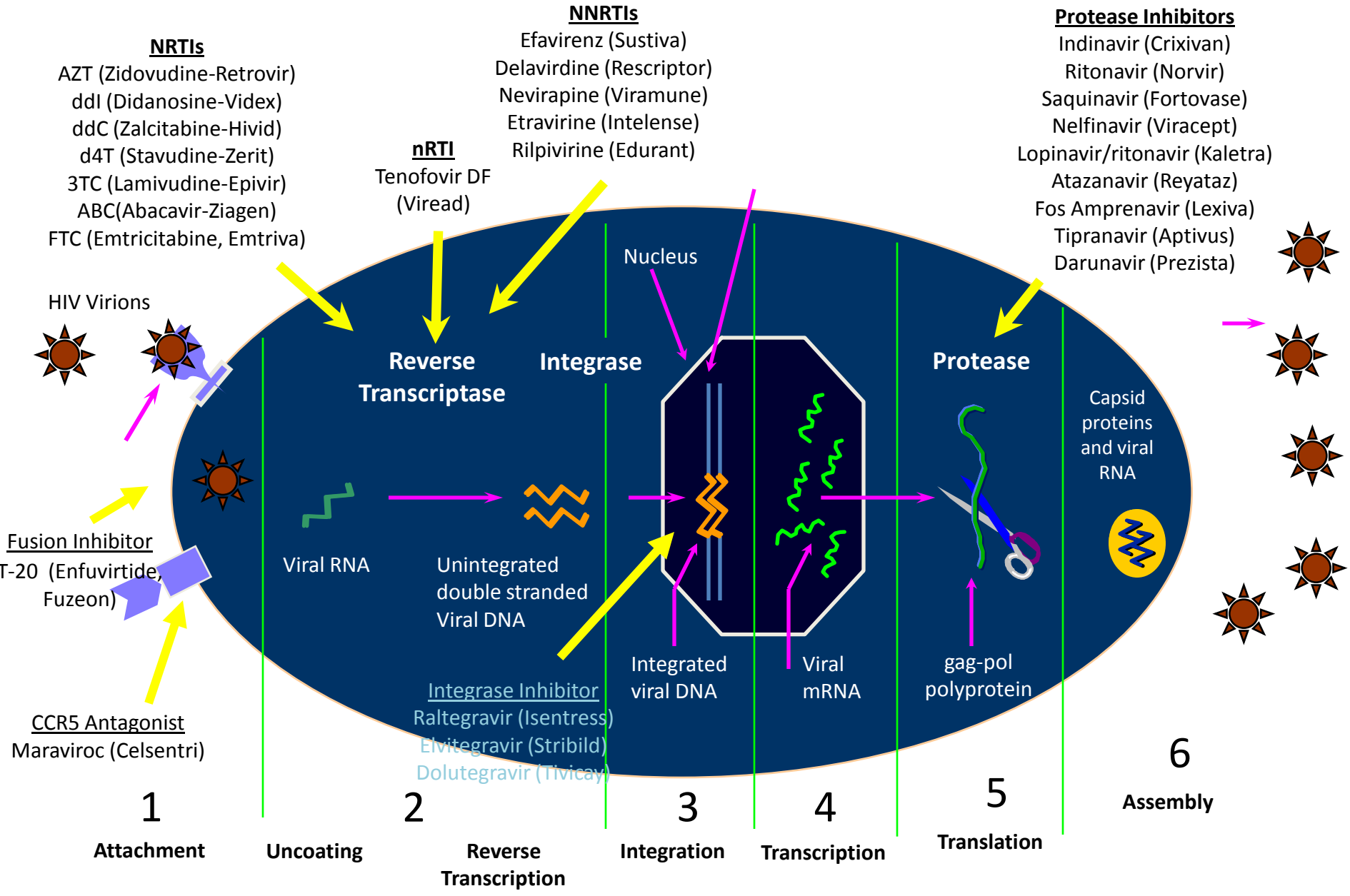
- HAART stands for Highly Active Antiretroviral Therapy
- HAART combines drugs from different classes, slowing HIV replication down at different stages
- HAART is also called combination therapy, a "cocktail," or a "regimen"

Examples of HAART regimens:

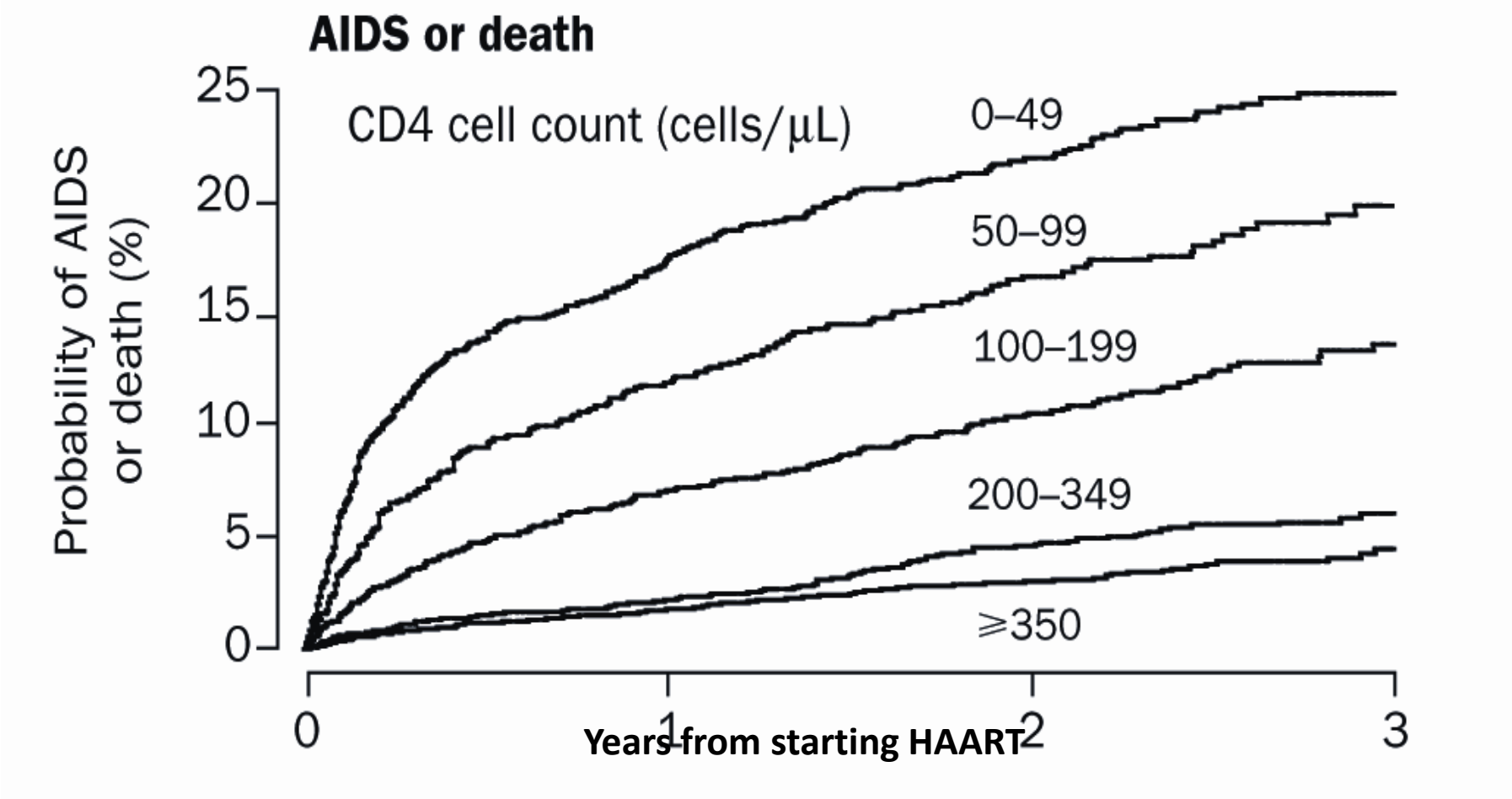


Reference: AIDS*info*: A Service of the U.S. Department of Health and Human Services. HIV and its treatment: what you should know. February 2008. Available at: http://www.aidsinfo.nih.gov/contentfiles/HIVandItsTreatment_cbrochure_en.pdf. Accessed June 12, 2008.

HIV replication cycle and sites of drug activity



Analysis of 13 cohort studies: effect of baseline CD4 count on response to initial ART



Egger et al. Lancet 2002; 360:119-30.

When to Start ART

ART is recommended for treatment of HIV infection and prevention of transmission of HIV regardless of CD4 cell count

- **Lack of demonstrated harm with early initiation, cost effective, clinically beneficial**
- **ART is cost-effective in resource-rich and – poor countries**

- **The patient must be willing and ready to initiate therapy; patients not ready to start ART should remain in clinical care, with regular monitoring and ongoing discussion about need for ART**

When to Start ART
According to clinical condition

- **Acute phase of primary HIV infection, regardless of symptoms**
- **Preferably within first 2 weeks of diagnosis of opportunistic infections**

What Treatment to Start

- **ART is considered lifelong; sustained viral suppression is foundation for immune recovery, optimal health, and prevention of resistance and transmission.**

- **Maximize adherence and minimize toxicity: Goal is to treat with effective, well-tolerated therapy, with limited drug interactions and effects on comorbid conditions.**

- **Base selection on baseline resistance testing and patient characteristics and preferences**

What Treatment to Start

- **First-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI)**

- **TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART .**

- **If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following alternative options is recommended: ° AZT + 3TC + EFV ° AZT + 3TC + NVP ° TDF + 3TC (or FTC) + NVP**

Recommended Initial ART Regimens: INSTI plus 2 nRTIs

INSTI plus 2 nRTI Combinations	Rating	Comments
DTG plus TDF/FTC	AIa	DTG is dosed once daily. Associated with modest increases in creatinine level due to inhibition of creatinine secretion
DTG plus ABC/3TC	AIa	No evidence that ABC/3TC performs less well at HIV-1 RNA levels >100 000 copies/mL when given with DTG. A fixed-dose combination is in late-stage development.
EVG/cobi/TDF/FTC	AIa	Once-daily fixed-dose combination. Cobi is associated with modest increases in creatinine level; has drug interactions similar to RTV.
RAL plus TDF/FTC	AIa	RAL is taken twice daily.

Recommended Initial ART Regimens: NNRTI plus 2 nRTIs

NNRTI plus 2 nRTI Combinations	Rating	Comments
EFV/TDF/FTC	AIa	EFV central nervous symptoms may persist beyond 2-4 weeks, but is no longer contraindicated for use in pregnant women
EFV plus ABC/3TC	AIa	EFV central nervous symptoms may persist beyond 2-4 weeks, but is no longer contraindicated for use in pregnant women
RPV/TDF/FTC	AIa	Once-daily fixed-dose combination. RPV-based therapy is not recommended in patients with baseline HIV-1 RNA levels > 100 000 copies/mL

Recommended Initial ART Regimens: RTV-boosted PI plus 2 nRTIs

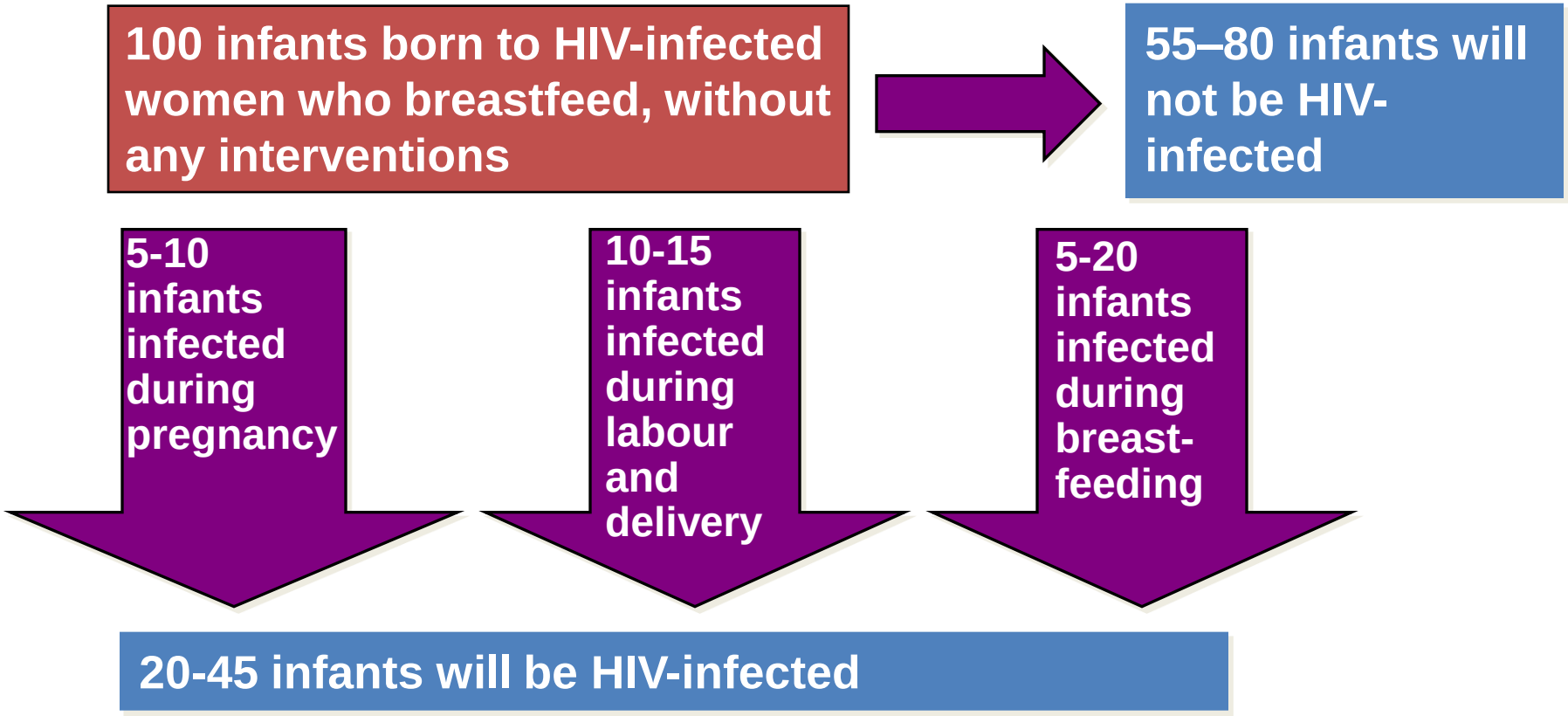
RTV-boosted PI plus 2 NRTI Combinations	Rating	Comments
ATV plus TDF/FTC	AIa	ATV is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.
ATV plus ABC/3TC	AIa	ATV is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.
DRV plus TDF/FTC	AIa	During initial therapy, 800 mg of DRV is given once daily with 100 mg of RTV given once daily

Pregnancy

- **ART should be initiated in all HIV-infected women who become pregnant; ZDV/3TC plus either RTV-boosted LPV or RTV-boosted ATV are preferred**

- **ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continued lifelong.**

HIV-Exposed Infant Outcomes



Reducing MTCT

MTCT can be reduced by 40-70% through core PMTCT interventions

- **In industrialized countries the rate of MTCT has been reduced to 2%**

Recommendations for Monitoring Upon Initiation of or Change in ART

HIV-1 RNA levels:

- **Monitor at approximately 4 weeks after treatment initiation or change;**
- **Monitor every 3 months to confirm suppression of viremia to below the limitation of quantification of sensitive commercial assays**

CD4 cell count:

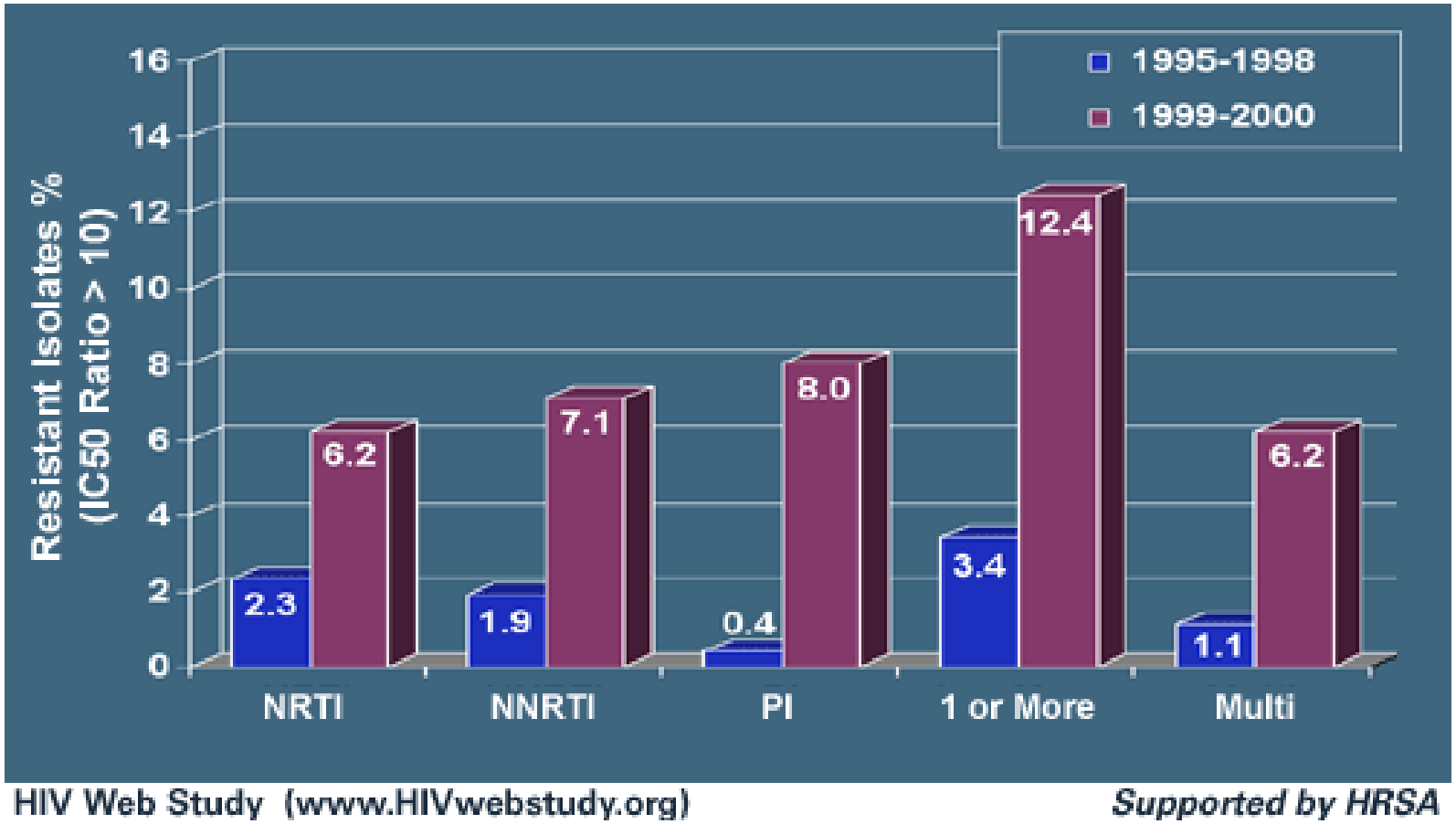
- **Monitor every 3 months after initiation of ART, especially for patients with cell counts of <200 µL;**
- **results will determine need to initiate or discontinue primary opportunistic infection prophylaxis**

Monitoring

- **Baseline genotypic testing for resistance in all treatment-naive patients and in cases of confirmed virologic failure.**
- **Routine therapeutic drug monitoring is not recommended, though selected patients may benefit.**
- **Laboratory monitoring for ART toxicity is recommended, guided by presence or absence of co-morbidities and by components of the regimen.**

Resistance in treatment-naïve individuals is becoming more common

Recently Infected, ART Naïve, United States



Little SJ, Holte S, Routy JP, et al. N Engl J Med. 2002;347:385-94

Antiretroviral Resistance Testing: Guidelines for Implementation

Clinical Setting/ Recommendation	Rationale
Recommended:	
•Virologic failure during ART	Determine role of resistance in drug failure and maximize the number of active drugs in the new regimen
•Suboptimal suppression of viral load (VL) after initiation of ART	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen
•Acute (primary) HIV infection	Determine if resistant virus was transmitted; select regimen accordingly
•Chronic HIV infection before starting ART	Assays may not detect minor resistant species, but some resistance mutations may persist for years. Consider testing early after diagnosis of HIV infection.
Usually not recommended:	
•After discontinuation of drugs	Resistance mutations may become minor species in the absence of selective drug pressure
•Plasma VL <1,000 copies/mL	Resistance assays unreliable if VL is low

Adapted from DHHS, Antiretroviral Guidelines, October 6, 2005

Turning to antiretrovirals for prevention

The use of anti-retrovirals for prevention by

1. **HIV-negative individuals to reduce their risk of infection**
   - **Post-exposure prophylaxis (PEP)**
   - **Pre-exposure prophylaxis (PrEP)**
     - **Oral PrEP (pills)**
     - **Topical PrEP (ARV-based microbicides)**

2. **HIV-positive individuals to reduce their risk of transmitting HIV**
   - **Treatment as prevention**

Oral pre-exposure prophylaxis

- **Oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) should be offered as an additional prevention choice for key populations at substantial risk of HIV infection as part of combination HIV prevention approaches**

Post-exposure prophylaxis (PEP)

- **Post-exposure prophylaxis (PEP) should be available to all eligible people on a voluntary basis after possible exposure to HIV.**
- **A regimen for post-exposure prophylaxis for HIV with two drugs is effective, but three drugs are preferred**
- **TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis in adults and adolescents**
- **A full 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment**

Prevention

New prevention strategies

In the era of PrEP and treatment as prevention, do we still need vaccine?

Vaccine:

- **Given once**
- **Durable protection**
- **Cost-effectiveness**

Primary Prevention of HIV

- **"ABC": an HIV primary prevention strategy**
  - **A = Abstain**
  - **B = Be faithful to one partner**
    - **also called "mutual faithfulness" or "mutual monogamy"**
  - **C = Use condoms correctly and consistently (every time)**

Recent Advances in Antiretroviral Therapy

- ***incremental gains in convenience, tolerability, and insights into toxicity have added up to significant improvements in management of HIV disease***

Advances in Antiretroviral Therapy: Easier Regimens

- **Lower pill burden**
  - **Fixed dose combinations**
    - **TDF/FTC (*Truvada*)**
    - **ABC/3TC (*Epzicom*)**
    - **AZT/3TC (*Combivir*)**
    - **AZT3TC/ABC (*Trizivir*)**
  - **Fewer pills for same effect**
    - **efavirenz**
    - **nelfinavir**
    - **fosamprenavir**
    - **lopinavir/ritonavir**
    - **saquinavir**
- **Once-daily dosing**
  - **tenofovir**
  - **3TC, FTC**
  - **abacavir**
  - **ddI**
  - **efavirenz**
  - **atazanavir**
  - **fosamprenavir (w/ ritonavir)**
  - **saquinavir (w/ ritonavir)**
  - **lopinavir/ritonavir**

- **Fewer food restrictions with newer agents and with ritonavir boosting of protease inhibitors**

Advances in Antiretroviral Therapy: Improvements in Toxicity

- **New drugs with less toxicity**
  - Tenofovir: no dyslipidemia compared with d4T
  - Atazanavir: no dyslipidemia compared with other PIs

- **Improved Understanding of Toxicities**
  - Nevirapine toxicity: identification of high-risk groups
    - women CD4 >250 cells/mm^3
    - men CD4 >400 cells/mm^3
  - Mitochondrial toxicity as basis for many long-term toxicities
  - Clarification of which NRTIs are most likely to cause mitochondrial toxicity (d4T, ddI, ddC)
  - Partial clarification of lipodystrophy

Unmet Needs

- **Widespread testing and linkage to care**, enabling people living with HIV to access treatment early.
- **Broad support for people living with HIV to remain engaged in comprehensive care**, including support for treatment adherence.
- **Universal viral suppression** among people living with HIV.
- **Full access to comprehensive PrEP services** for those whom it is appropriate and desired, with support for medication adherence for those using PrEP.

Unmet Needs

- **to develop long-acting therapies that—unlike current antiretrovirals, which require daily dosing—could be taken only once a week, once a month, or even less often**
- **The three types of agents under study are long-acting drugs, broadly neutralizing antibodies, and therapeutic vaccines.**
- **include longer-acting pills as well as alternative formulations such as injections, patches, and implants**
- **two investigational long-acting HIV drugs, rilpivirine LA and cabotegravir LA,**

Unmet Needs

- **Antibodies are good candidates for treatment because they have few side effects and can be modified to ensure they last a long time in the body, suggesting that dosing could be every other month or even less often**
- **scientists are engineering changes to known bNAbs to optimize them for HIV treatment and prevention applications**

Unmet Needs

- **Unlike a vaccine designed to prevent HIV infection, a therapeutic vaccine would be given to people already infected with the virus**
- **Such an approach could lead to sustained viral remission, meaning treatment or vaccination that would result in prolonged undetectable levels of HIV without regular antiretroviral therapy**
- **Researchers also are attempting to target other parts of the HIV lifecycle. E.g., the experimental entry inhibitor fostemsavir blocks the gp120 receptor of HIV, development of capsid assembly inhibitors, which halt construction of the viral capsid, that encloses HIV's genetic material.**

Unmet Needs

- **Evaluations of interventions to improve access to reliable early infant diagnostics, including rapid test protocols.**

- **Evaluations and/or validation of simplified, standardized diagnostic tools to assess neurocognitive and physical development in HIV-exposed infected or uninfected infants, children and adolescents in resource-limited settings.**

- **Studies evaluating interventions and optimal models for integrating paediatric HIV services with maternal, newborn and child health and other health services.**

- **Studies evaluating interventions and optimal models for promoting early post-natal and long-term programme retention and reducing loss to follow-up.**

Conclusion

- Virologic suppression and immune restoration remain the most important goals of HIV disease management
- Early, intensified, widespread, and uninterrupted treatment is best option for controlling the epidemic
- With increasing longevity of HIV-infected patients, focus is shifting toward whole health patient care
- Comprehensive initial laboratory assessment and patient workup ensures the best care

Many Many Thanks for Patience