



British Columbia
Centre for excellence
in HIV/AIDS



When and What to Start With?

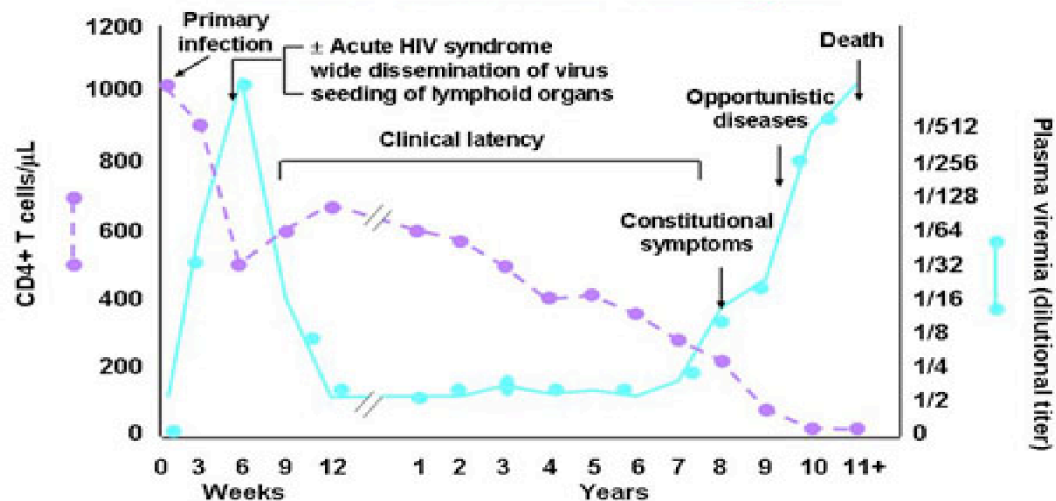
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Objectives

- When to start ARV's
- What to start with
- Monitoring of patient on ARV's
- Treatment failure

Depletion of Circulating CD4+ T Cells Results in Progressive Immune Deficiency

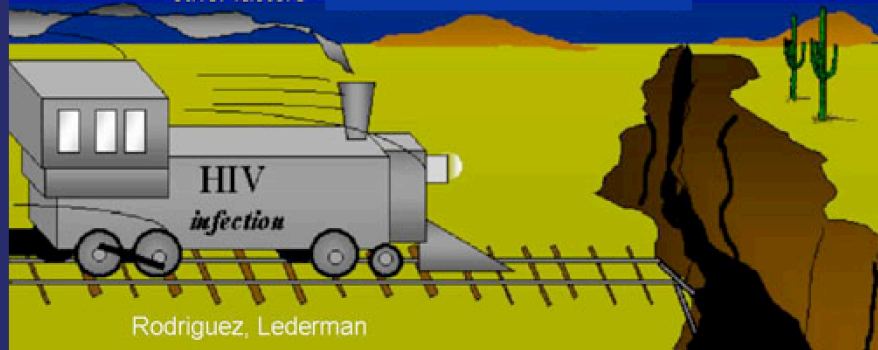


- This graph displays the natural history of the HIV disease.
- During acute infection there is high levels of HIV RNA in plasma, and CD4's counts decreased. This period of acute infection or sero-conversion can last up to 12 weeks. Generally it is a period of time when individuals are more infectious.
- Afterwards there is period of clinical latency, where the pVL levels remain relatively stable and a steady decreased on the CD4's count occurs.
- When CD4 counts reach levels below 200 cell/ml patients become increasingly at risk for acquiring opportunistic infections or other AIDS related events and eventually death.

A Modified Coffin Model

Developing AIDS is like an impending train wreck:

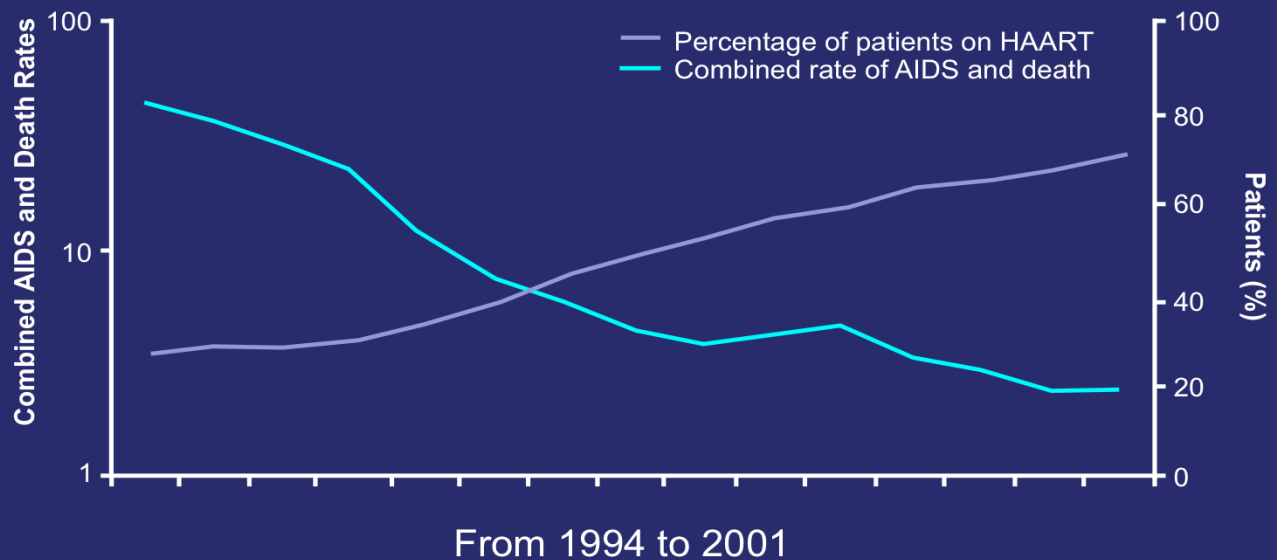
- The CD4 count is the distance from the cliff
- Viral load is the fuel
- Speed of the train depends on:
 - Engine gear ratio (host factors)
 - Fuel mix (ie, immune activation driven by viremia and other factors –



Developing AIDS is like a train wreck. The CD4+ T-cell count is the distance from the cliff. But rather than determining the pace of CD4+ T-cell decline, viral load is the fuel that drives the engine. The speed of the train depends on a variety of factors that include engine gear ratio, which in this instance could be host related factors; particularly the immune activation driven by viremia; and other factors, such as other microbial TLR ligands.

EuroSIDA: AIDS and Death Since Introduction of HAART

- Morbidity and mortality across Europe, Israel, and Argentina: ~ 10,000 patients



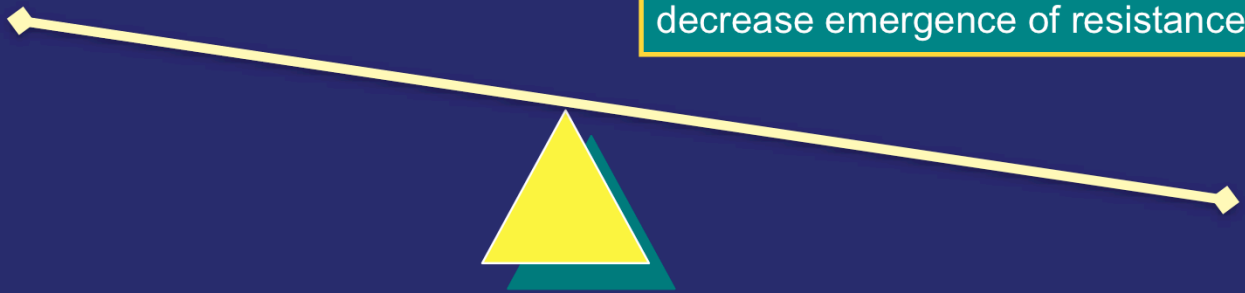
Mocroft A, et al. Lancet. 2003;362:22-29.

- Successful antiretroviral therapy (ART) is associated with dramatic decreases in AIDS- defining conditions and their associated mortality.
- Expansion of treatment options and evolving knowledge require revision of guidelines for the initiation and long-term management of ART in adults with HIV infection.

When to Start Therapy: Balance Tipping in Favor of Earlier Initiation

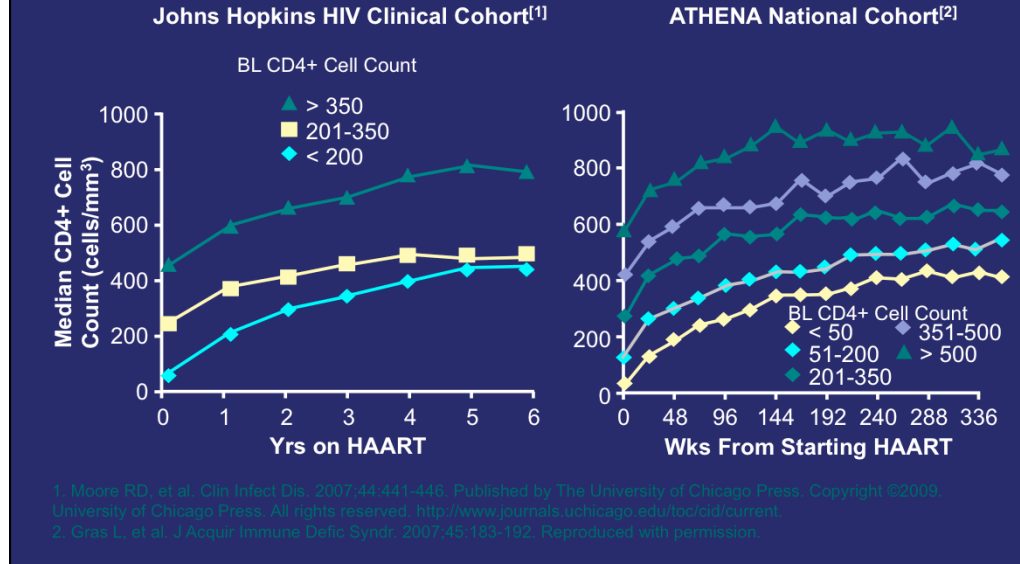
- Drug toxicity
- Preservation of limited Rx options
- Cost

- Harmful effects of uncontrolled viremia at all CD4 levels
- Increased treatment options: improved potency, tolerability, durability, simplicity
- Increased ability to suppress multidrug resistance virus and decrease emergence of resistance



- Advances in ART continue to shift the therapeutic risk-benefit balance to earlier treatment.
- Improvements in potency, toxicity and tolerability, and pill burden allow for durable viral suppression for most patients.
- The risks associated with ART have decreased, whereas concerns regarding the risks of long-standing untreated viremia have increased.
- Uncontrolled HIV replication and immune activation lead to a chronic inflammatory state, resulting in end-organ damage and co-morbid conditions not previously thought to be associated with HIV infection.

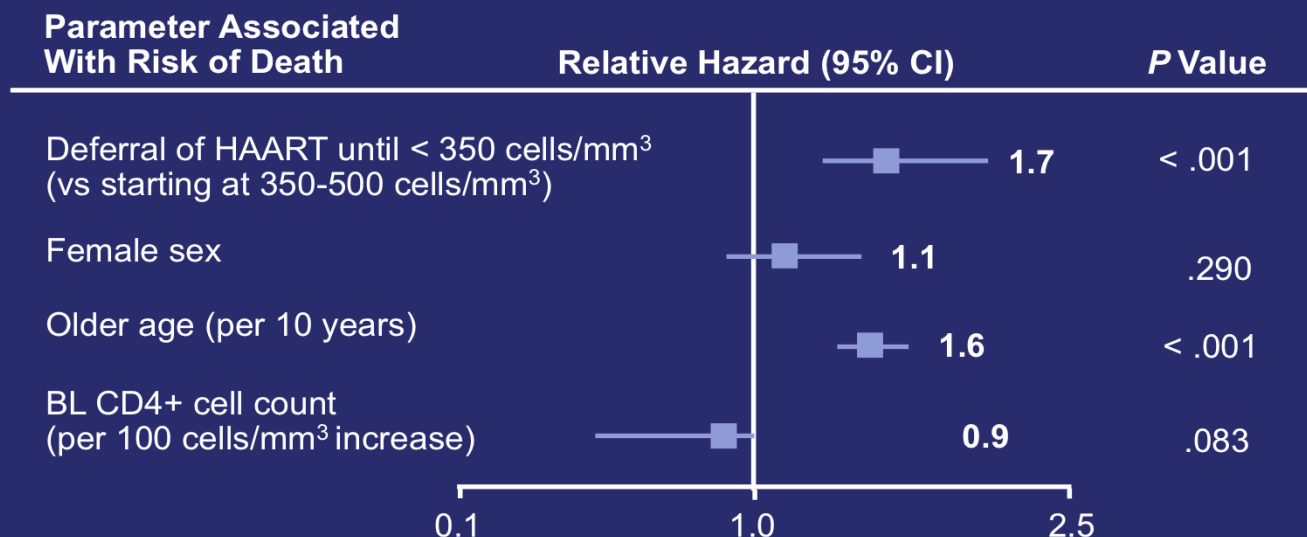
Likelihood of Achieving Normal CD4+ Cell Count on ART Depends on BL Level



**** BL, baseline; HAART, highly active antiretroviral therapy**

- This slide depicts the results of 2 different cohort studies that asked the question, is there a difference in how high CD4+ cell counts become during therapy based on CD4+ cell counts at the time of initiation of therapy? The results of both studies were quite consistent with one another.
- Data from the Johns Hopkins HIV clinical cohort shows that the CD4+ cell count increases during therapy, approx. 250-350 cells/mm³ regardless of where one starts. Therefore, if patients start treatment with a CD4+ cell counts of 50 cells/mm³, they will ultimately reach a CD4+ cell count of approximately 300-400 cells/mm³. The only patients who achieved CD4+ cell counts of 600-700 cells/mm³ were patients who initiated therapy at CD4+ cell counts of 400-500 cells/mm³, thereby supporting the idea of earlier initiation of therapy.
- Data from the ATHENA National Cohort include a broader range of baseline CD4+ cell counts. The absolute CD4+ cell count increase is approximately the same regardless of the baseline count and appears to plateau after an increase of approximately 300-350 cells/mm³. This result shows that if patients start therapy at a very low CD4+ cell count, it is unlikely that they will be able to restore CD4+ levels to a “normal” range. Therefore, earlier initiation of therapy is more likely to achieve a normal CD4+ cell count than deferred initiation of therapy.

NA-ACCORD: Survival Benefit With Earlier vs Deferred HAART



- Increased relative hazard of death with deferral of HAART remained unchanged when adjusted for IDU or for HCV coinfection, which were both independent predictors of mortality

Kitahata MM, et al. ICAAC/IDSA 2008. Abstract H-896b.

- In a cohort of 17 517 asymptomatic HIV-infected persons, initiating HAART at a CD4 cell count greater than 500/ μ L decreased mortality by 94%.
- Initiating HAART at a CD4 cell count between 351 and 500/ μ L decreased mortality by 69%, although the numbers of deaths were low in both groups. The majority of deaths were from non-AIDS conditions.

SMART: Immediate Therapy Reduces Risk of OD, Serious Non-AIDS Events

- Immediate group experienced substantially fewer events compared with deferred group
 - Excess risk associated with deferring therapy:
5.4 events/100 person-yrs

Event, n (Rate per 100 Person-Yrs)	Deferred Arm (n = 228)	Immediate Arm (n = 249)	HR (DC/VS)	95% CI	P Value
OD/death	15 (4.8)	5 (1.3)	3.5	1.3-9.6	.02
OD only	11 (3.5)	4 (1.1)	3.3	1.0-10.3	.04
Serious non-AIDS events	12 (3.9)	2 (0.5)	7.0	1.6-31.4	.01
Composite*	21 (7.0)	6 (1.6)	4.2	1.7-10.4	.002

*Fatal and nonfatal OD plus serious non-AIDS events.

Emery S, et al. J Infect Dis. 2008;197:1133-1144.

** CI, confidence interval; HR, hazard ratio; OD, opportunistic disease.

- The SMART study compared major clinical outcomes in patients not receiving antiretroviral therapy at study entry who either initiated early antiretroviral therapy (when CD4+ cell count > 350 cells/mm³) or deferred initiation (until CD4+ cell count < 250 cells/mm³)
- In this sub-study they showed that the patients who were randomized to the immediate therapy arm had a reduced risk of opportunistic disease and serious non-AIDS events relative to patients who deferred therapy until reaching lower CD4+ cell counts.
- The first row in the table includes data on opportunistic disease or death. In the deferred arm, there were 15 events, representing 4.8 events per 100 person-years of follow-up compared with only 5 events among patients who initiated and maintained therapy in the immediate arm, representing 1.3 events per 100 person-years. This is a 3.5-fold increased risk among patients who deferred therapy with a statistically significant *P* value of .02.
- In addition, opportunistic disease alone or serious non-AIDS events alone were also statistically significantly in favor of initiating therapy, with fewer events occurring in the group that started and sustained therapy compared with patients who deferred and interrupted therapy.
- Finally, for the composite endpoint there were 21 outcomes among 228 patients or 7 per 100 person-years, vs only 6 outcomes among 249 patients in the immediate arm, or 1.6 per 100 person-years, reflecting a statistically significant difference in favor of those who initiated therapy.

For more information, go online to: <http://clinicaloptions.com/HIV/Journal%20Options/Articles/Emery-JID-2008/Capsule.aspx>



Thompson M, Aberg J, Cahn P, Montaner J, et al.
JAMA. 2010;304:321-333

REVIEW
CLINICIAN'S CORNER

Antiretroviral Treatment of Adult HIV Infection

2010 Recommendations of the International AIDS Society-USA Panel

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Context Recent data regarding the consequences of untreated human immunodeficiency virus (HIV) infection and the expansion of treatment choices for antiretroviral-naïve and antiretroviral-experienced patients warrant an update of the International AIDS Society-USA guidelines for the use of antiretroviral therapy in adults with HIV infection.

Objectives To review new data in HIV medicine and provide updated recommendations for management of HIV-infected adults, using antiretroviral drugs and laboratory monitoring tools available in the international, developed-world setting. This report provides guidelines for when to initiate antiretroviral therapy, selection of appropriate initial regimens, patient monitoring, when to change therapy, and what regimens to use when changing.

Data sources and study selection A panel with expertise in HIV research and clinical care reviewed relevant data published or presented at selected scientific conferences since the last panel report through April 2010. Data were identified through a PubMed search, review of scientific conference abstracts, and requests to antiretroviral drug manufacturers for updated clinical trials and adverse event data.

Data extraction and synthesis New evidence was reviewed by the panel. Recommendations were drafted by section writing committees and reviewed and edited by the entire panel. The quality and strength of the evidence were rated and recommendations were made by full-panel consensus.

Conclusions Patient readiness for treatment should be confirmed before initiation of antiretroviral treatment. Therapy is recommended for asymptomatic patients with a CD4 cell count $\geq 500/\mu\text{L}$, for all symptomatic patients, and those with specific conditions and comorbidities. Therapy should be considered for asymptomatic patients with CD4 cell count $>500/\mu\text{L}$. Components of the initial and subsequent regimens must be individualized, particularly in the context of concurrent conditions. Patients receiving antiretroviral treatment should be monitored regularly; treatment failure should be detected and managed early, with the goal of therapy, even in heavily pretreated patients, being HIV-1 RNA suppression below commercially available assay detection limits.

JAMA. 2010;304(2):321-334 www.jama.com

METHODS
The panel was convened in 1995 to develop evidence-based recommendations for ART for HIV-infected adults in developed-world settings.² Members are appointed by International AIDS Society-USA according to clinical and research expertise. Current panel members do not participate in pharmaceutical marketing.

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JAMA. July 21, 2010;304(3):321-334

CME available online at
www.jamaonlinecme.com
 and questions on p. 333.

- The International AIDS Society panel, comprised of HIV research and clinical care experts, reviews relevant data published or presented at selected scientific conferences and provide updated guidelines every 2 years.

Rationale for Early Initiation of Therapy

- Uncontrolled HIV replication, immune activation and inflammation associated with 'non-AIDS' illnesses
 - Cardiovascular, hepatic, renal, malignancies
 - ART and high CD4 associated with decreased disease incidence
- Patients not on ART with CD4 counts $< 500/\mu\text{L}$ have greater morbidity and mortality than those with viral suppression
- Increasing evidence of detrimental effects of uncontrolled viremia at CD4 cell counts $> 500/\mu\text{L}$

Rationale for Early Initiation of Therapy: Special Circumstances

- ART initiation is recommended regardless of CD4 cell count in some circumstances

- ✓ High viral load ($>100,000$ c/mL) or rapidly declining CD4 ($>100/\mu\text{L}$ per year)
- ✓ Pregnancy
- ✓ HIV-associated nephropathy
- ✓ Active HBV or HCV co-infection
- ✓ Active or high risk for cardiovascular disease
- ✓ Opportunistic infections, including TB
- ✓ Age $>$ than 50 years
- ✓ Symptomatic primary infection
- ✓ High risk for HIV transmission

When to Start Antiretroviral Therapy

Measure	Recommendation
Asymptomatic HIV Infection	
CD4 \leq 500/ μ L	Therapy recommended
CD4 > 500/ μ L	Therapy should be considered and decision individualized No CD4 cell count above which therapy is contraindicated; evidence increases as CD4 declines

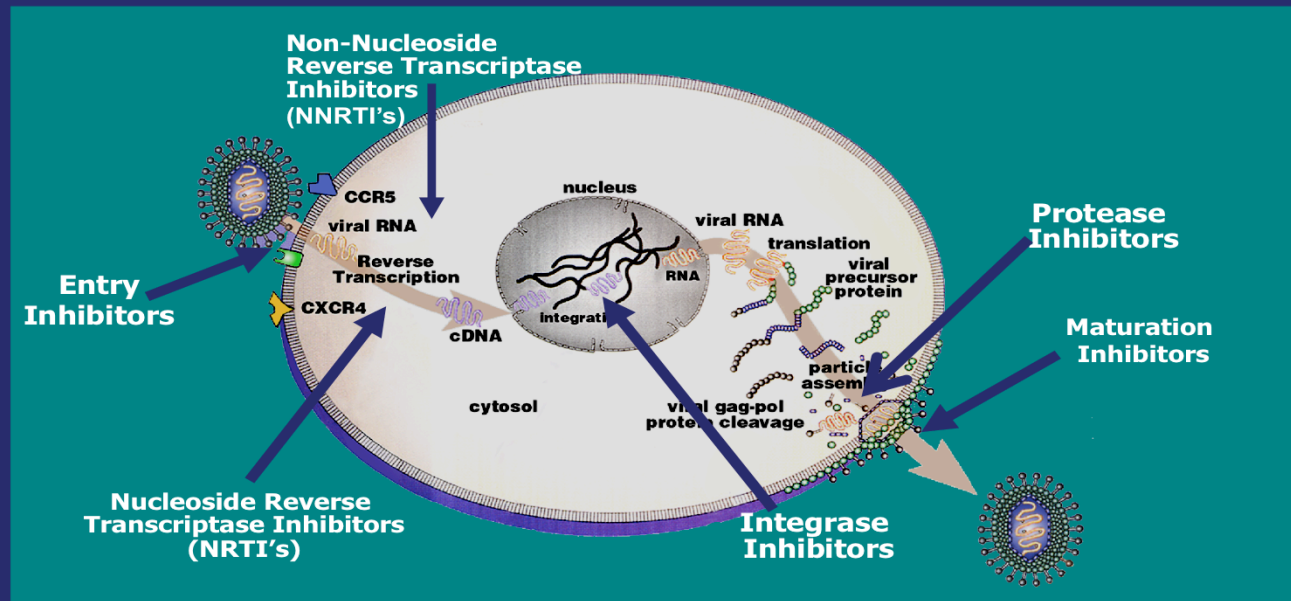
Present Antiretroviral Guidelines, including the most recent BC CfE, recommend initiation of antiretroviral therapy in all patients with CD4's count below 500 cell/ml, and in all of those with CD4's counts over 500 cell/ml who have :

- High viral load (>100,000 c/mL) or rapidly declining CD4 count(100/ μ L per year)
- Pregnancy
- HIV-associated nephropathy
- Active HBV or HCV co-infection
- Active or high risk for cardiovascular disease
- Opportunistic infections, including TB
- Age > than 50 years
- Symptomatic primary infection
- High risk for HIV transmission

Objectives

- When to start ARV's
- What to start with
- Monitoring of patient on ARV's
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TARGETS FOR HIV INHIBITION



- The above slide displays a CD4+ T cell and the points at which the various drug classes target HIV inhibition.
- There are several drug classes available that target different points in the cycle of viral replication:

The first class of drugs are the Nucleoside Reverse Transcriptase Inhibitors (NRTI's)

The second class of drugs are the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)

The third class of drugs are the Protease Inhibitors (PI's)

The fourth class of drugs are the Entry Inhibitors which includes the fusion inhibitor T20, and the CCR5 antagonist Maraviroc.

Integrase Inhibitors are a relatively new class of drugs

Maturation Inhibitors are a class of drugs, however, there are currently no available drugs within this class

Antiretroviral Agents Approved

Nucleoside RTIs

- Zidovudine (ZDV)
- Didanosine (ddI)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

Nucleotide RTI

- Tenofovir DF (TDF)

Nonnucleoside RTIs

- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFZ)
- Etravirine (ETV)

Integrase Inhibitor

- Raltegravir (RAL)

Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

Fusion Inhibitor

- Enfuvirtide (T-20)

CCR5 Antagonist

- Maraviroc (MVC)

N.B.: Six fixed-dose combinations are approved:

ZDV + 3TC; ZDV + 3TC + ABC; ABC + 3TC;
FTC + TDF; LPV + RTV; TDF + FTC + EFV

- The diagram displays the classes and drug names of currently approved antiretroviral agents.
- The most common drugs groups presently use, are highlighted with the circles.

Antiretroviral Drugs Fixed Dose Combination

- Kivexa (3TC - Abacavir)
- Truvada (Tenofovir - FTC)
- Atripla (Truvada- Efavirenz)
- Combivir (AZT- 3TC)
- Trizivir (AZT- 3TC - Abacavir)

- The highlighted antiretroviral agents are the most commonly used fixed combinations drugs.
- Kivexa is a combination of 2 NRTI's (Lamivudine or 3TC and Abacavir)
- Truvada is a combination of 2 NRTI's (Tenofovir and Emtricitavine)
- Atripla is the only fixed dose medication with a combination of two different classes of drugs (NRTI's , Truvada and the NNRTI's Efavirenz)

Recommended Components of Initial ART

Backbone	Third Agent
<p>TDF/FTC (Truvada)</p> <p>Alternative: ABC/3TC (Kivexa)</p>	<p>EFAVIRENZ (Atripla) or ATAZANAVIR/ritonavir</p> <p>Alternatives IntI: RALTEGRAVIR PI: DARUNAVIR/ r</p> <p> <i>EI: MARAVIROC PI: LOPINAVIR/ r PI: FOSAMPRENAVIR /r</i> </p>

PI mono-therapy and dual therapy strategies not recommended for clinical practice

Modified from Thompson M, Aberg J, Cahn P, Montaner J, et al. JAMA. 2010;304:321-333

- These are the latest BC CfE guidelines recommendations for initiation of antiretrovirals, modified from the IAS 2010 therapeutic guidelines
- The backbone component is usually Truvada, or, alternatively Kivexa in combination with a third agent.
- The third agent is usually Efavirenz or Atazanavir/ritonavir.
- Alternative options are the Integrase Inhibitor Raltegravir or the boosted Protease Inhibitor Darunavir
- Also Maraviroc (entry inhibitor), and the protease inhibitors Kaletra and Boosted Fosamprenavir are alternative options

Dual NRTI Component Recommended

Recommended

Tenofovir/emtricitabine (Truvada)

- Available as fixed-dose combination alone and with efavirenz.
- Once daily
- Low genetic barrier to resistance (emtricitabine)
- Renal dysfunction, decreased bone mineral density associated with tenofovir

Alternative

Abacavir/lamivudine (Kivexa)

- Available as fixed-dose combination
- Once daily
- Weaker antiviral efficacy in treatment-naïve patients with baseline HIV-1 RNA >100 000 copies/mL than tenofovir/ emtricitabine
- Low genetic barrier (lamivudine)
- Need to screen for HLA-B*5701b to reduce risk of abacavir hypersensitivity
- Abacavir may be associated with increased cardiovascular risk

- Truvada is generally preferred as first option, since Abacavir has been associated with higher incidence of cardiovascular events and virological failures in patients with high plasma viral load

Reference 1: Sabin C et al. *Do thymidine analogues, abacavir, didanosine and lamivudine contribute to the risk of myocardial infarction? The D:A:D study. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston. Abstract 957c, 2008.*

Reference 2: Daar E et al. *ACTG 5202: final results of ABC/3TC or TDF/FTC with either EFV or ATV/r in treatment-naïve HIV-infected patients. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 59LB, 2010.*

- Truvada can cause renal toxicity associated with albuminuria and Fanconie like syndrome. Close renal monitoring is advised, and if possible avoid in patients with renal impairment due to other co-morbidities.
- Tenofovir FTC and 3TC are also active against Hepatitis B virus.
- All patients receiving Kivexa should have an HLB5701 test at baseline.

Advantages and Disadvantages of NNRTIs (Efavirenz) for Initial Therapy

- | | |
|---|---|
| <ul style="list-style-type: none"> • Potential advantages <ul style="list-style-type: none"> – Convenient, simple dosing – Virologic superiority of EFV + 2 NRTIs vs LPV/RTV + 2 NRTIs^[1] – Durable efficacy^[2,3] – Fewer metabolic AEs (dyslipidemia, insulin resistance) than PIs – Consistent activity at high pretreatment HIV-1 RNA and low pretreatment CD4^[1,4] – Preserve PI options for future use | <ul style="list-style-type: none"> • Potential disadvantages <ul style="list-style-type: none"> – Low genetic barrier to resistance – Use EFV with caution in women of childbearing potential – CNS AEs of EFV may limit use in small number of patients – Some providers avoid EFV in patients with psychiatric illness and substance abuse – Potential for rash, hepatotoxicity – Cross-resistance among first-generation agents |
|---|---|

1. Riddler SA, et al. N Engl J Med. 2008;358:2095-2106. 2. Arribas JR, et al. J Acquir Immune Defic Syndr. 2008;47:74-78. 3. Pozniak AL, et al. J Acquir Immune Defic Syndr. 2006;43:535-540. 4. Ribaudo HJ, et al. J Infect Dis. 2008;197:1006-1010.

AE, adverse event; CNS, central nervous system; EFV, efavirenz; LPV, lopinavir; RTV, ritonavir.

- The alternative to PI-based regimens is the NNRTI class, particularly efavirenz. Potential advantages of an efavirenz-based regimen include the possibility of convenient, once-daily dosing with fewer pills. In. The NNRTIs also have durable efficacy with fewer adverse metabolic events such as lipid abnormalities, insulin resistance, and other toxicities that are associated with PIs.
- There are also disadvantages to NNRTI-based regimens. NNRTIs have a low genetic barrier to resistance, meaning that in patients who experience virologic failure on an NNRTI-based regimen, there is a greater chance of developing resistance-associated mutations. Efavirenz is contraindicated in women of child-bearing potential and is also associated with well-known central nervous system adverse events that can create problems for a small number of patients initiating therapy with efavirenz-based regimens.

For more information, go online to:

<http://clinicaloptions.com/HIV/Journal%20Options/Articles/Riddler-NEJM-2008/Capsule.aspx>

Advantages and Disadvantages of Boosted PIs for Initial Therapy

- **Potential advantages**
 - QD dosing for 3 RTV-boosted PIs: ATV/RTV, DRV/RTV, LPV/RTV
 - Good virologic activity^[1-3]
 - High genetic barrier to resistance
 - Lack of CNS AEs
 - Use in women of childbearing potential
 - PI resistance uncommon at failure
 - Preserve NNRTIs for future use
- **Potential disadvantages**
 - All choices include RTV
 - No single co-formulated like NNRTI-based alternative
 - Hyperbilirubinemia and jaundice with ATV/r
 - Metabolic complications (hyperlipidemia)
 - Potential drug-drug interactions due to CYP450 metabolism, particularly with RTV

1. Molina JM, et al. Lancet. 2008;372:646-655. 2. Ortiz R, et al. AIDS. 2008;22:1389-1397.
3. Gathe J, et al. CROI 2008. Abstract 775.

AE, adverse event; ATV, atazanavir; CNS, central nervous system; DRV, darunavir; EFV, efavirenz; LPV, lopinavir; QD, once daily; RTV, ritonavir.

- Boosted PIs have many advantages, including the availability of once-daily dosing options for several PIs, very good virologic activity, and a high genetic barrier to resistance, meaning that even in patients who experience virologic failure on a PI-based first-line regimen, PI-associated resistance mutations are rarely observed.
- PIs also have several disadvantages. All of the currently recommended PIs are used with ritonavir boosting and there is no co-formulated single-tablet PI-based regimen. In addition, it is important to consider the toxicities associated with PI-based regimens, including metabolic complications and drug-drug interactions based on the cytochrome P450 system.

For more information, go online to:

<http://clinicaloptions.com/HIV/Conference%20Coverage/Retroviruses%202008/Tracks/Firstline/Capsules/775.aspx>

Other Third Agent Options

Lopinavir/r PI/r class

Extensive clinical experience
Only PI co-formulated with ritonavir (heat stable)
Can be given once daily in naive patients
Potential for hyperlipidemia and gastrointestinal adverse effects

Darunavir/r PI/r class

Once daily in treatment naïve patients but limited experience
Good efficacy in treatment experience patients with multidrug resistant virus

Raltegravir INSTI class

Twice daily
Low drug interaction potential
Low genetic barrier
Limited experience in naive patients, and efficacy in treatment-experienced patients

- Lopinavir is co-formulated with ritonavir (Kaletra), it can be given once a day (4 pill), and has been the first choice for first line therapy for many years. Recently , the new guidelines have put Kaletra as a second choice due to its toxicities, and due to new PI options with lower toxicity profiles and pill burden.
- In the Artemis trial, Darunavir with ritonavir was shown to be non inferior to Kaletra. It is a once a day PI option with a low toxicity profile. Some guidelines recommend this drug as first line option. Presently in the province of BC , it is recommended as an alternative for first line, since in combination with Raltegravir and Etravirene provides an excellent rescue treatment for patients with virological failure to prior therapies.
- Raltegravir belongs to a newer dug class (Integrase inhibitors) and it is given BID. It is a low toxicity profile potent antiretroviral drug. It has a low genetic barrier, and presently it is only recommended in the context of rescue therapy for patients with virological failure. It is a good option for patients with co-morbidites needing other medical therapies were drug interactions with ritonavir could be an issue.

Initial Regimen Considerations Summary

- Patient readiness to begin lifelong therapy
- Baseline assessment
 - Evaluate for hepatitis B or C virus coinfection, diabetes mellitus, hyperlipidemia, coronary artery disease, smoking, renal disease, other comorbid conditions
 - Consider drug interactions
 - Perform resistance testing
 - Perform HLA-B5701 test
 - Assess for pregnancy or risk thereof
 - Consider pill burden and adherence issues

- Working with pharmacists if invaluable in determining possible drug interactions.

Objectives

- When to start ARV's
- What to start with
- Monitoring of patient on ARV's
- Treatment failure

Patient Monitoring: Principles

- Viral load should be fully suppressed (< 40 copies/mL Taqman assay) regardless of treatment experience, by 24 weeks
- **CD4 cell counts and pVL should be monitored frequently after ARV's initiation**
- Frequent monitoring initially to detect and address failure and tolerability issues
- Assess need for OI prophylaxis, and IRS particularly on patients with CD4's $< 200/\text{mm}^3$
- Note that failure is defined by two consecutive viral loads > 250 c/mL

- The objective of antiretroviral therapy is to achieve virological suppression. In patients with very high viral load at baseline this can take longer. Generally undetectable viral load in plasma can be achieved by 6 months on treatment.
- CD4's count and pVL should be monitored on monthly bases after the initiation of HAART. Once the pVL is undetectable CD4's and pVL can be monitored every 3-6 months.
- Patients initiating ARV's with CD4's below 200 cell/ml, should be assess for possible opportunistic infections and IRS, Immune reconstitution syndrome. Most commonly they should be evaluated for PCP, TB, CMV retinitis, MAC, Toxoplasmosis and Lymphomas.
- If patients have viral rebounds after achieving virological suppression, the pVL should be repeated 2 to 4 weeks latter. Genotype testing should be completed in all pVL over 250 cell/ml.

Patient Monitoring

Parameter	Recommendation
HIV-1 RNA level	Relatively frequently (eg, every 4 wks) until <50 c/mL; and regularly (e.g., 3-4 times per year) thereafter
CD4 cell count	Once HIV-1 RNA is suppressed <50 c/mL for an extended period and CD4 is stable >350/ μ L, frequency of monitoring can be reduced to 4 x yearly
Resistance testing (≥ 250 c/mL)	When HIV-1 RNA decline is not optimal or when HIV-1 RNA is rebounding, on treatment
Viral tropism (R5, X4 or dual-mixed)	When maraviroc is being considered, off treatment
HLA-B*5701 screening	When abacavir is being considered (or at baseline)
Therapeutic drug monitoring	In selected cases

- Resistance testing can only be conducted if pVL is ≥ 250 c/mL
- Viral tropism should be request in patients when Maraviroc is consider as a treatment option. Presently it is done at the BC CfE laboratory and it should be requested in the patient's most recent detectable plasma viral load. Patients with CCR5 positive tropism are likely to respond to CCR5 inhibitors.
- HLA-B5701 is a genetic marker for patients that will developed Abacavir hypersensitivity reactions. There is an incidence of up to 5% of this being positive, particularly in the Caucasian population. It less common in patients of African origin. Abacavir should not be given to patients with positive HLA-B5701
- Therapeutic drug monitoring is the measurement of drug levels for certain treatments in selected cases.

Objectives

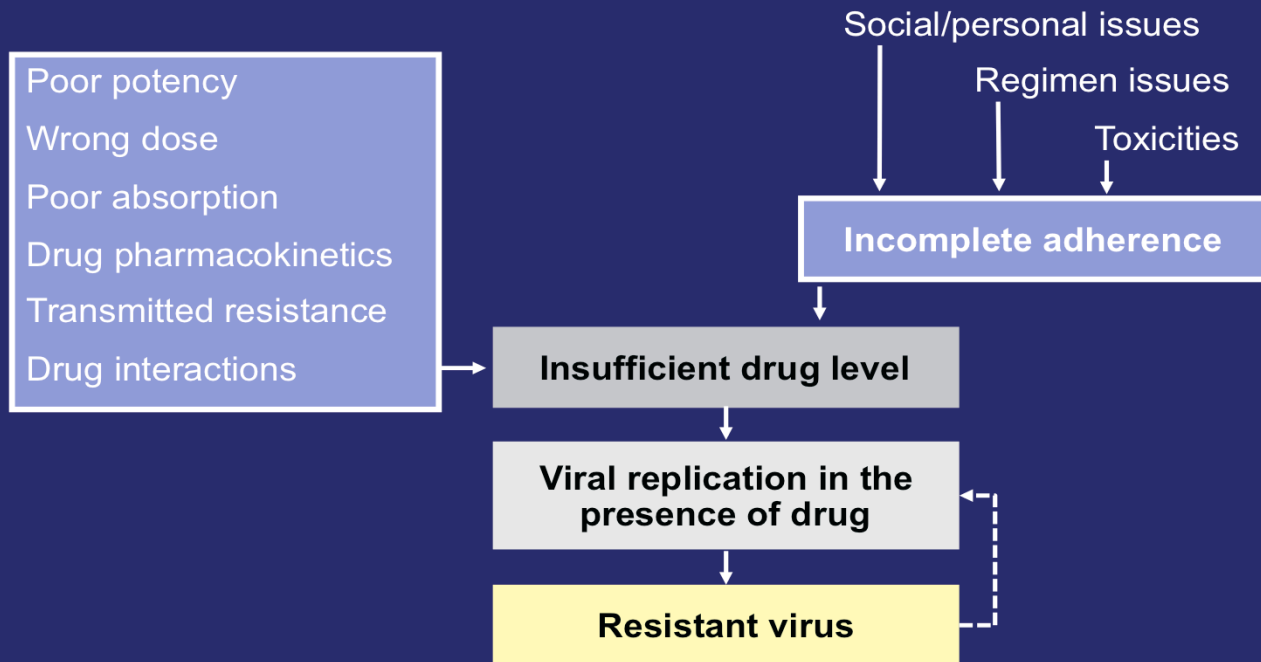
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What to Do When There Is Viral Rebound

- Assess possible causes for virologic failure
 - Incomplete adherence
 - Drug interactions
 - Intercurrent infections
 - Recent vaccinations
- Repeat to exclude measurement error or self-resolving transient viremia (blip)

- Always repeat pVL before altering treatment to exclude a blip or measurement error.

Causes of Treatment Failure

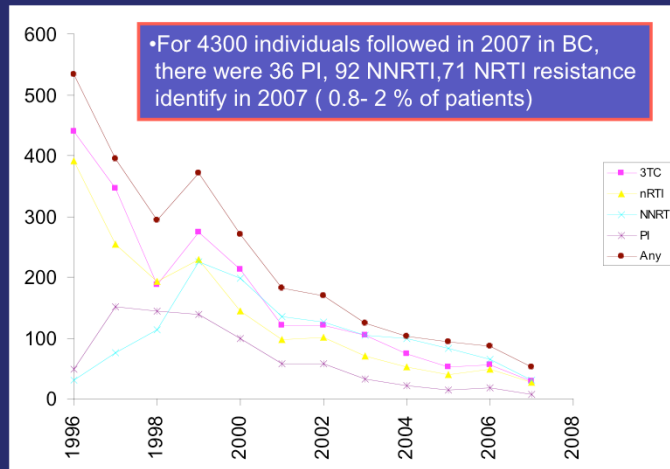


ART resistance testing. AETC National Resource Center.

ARV, antiretroviral.

- This slide reviews the causes for antiretroviral treatment failure. There are many factors that affect treatment failure and they are primarily associated with insufficient drug levels. If drug levels are not sufficient, viral replication occurs in the presence of the drug, thereby permitting emergence of resistant virus and subsequent treatment failure.
- Poor adherence is one cause of insufficient drug levels,. Frequently, there are social or personal issues that may be out of the patient's control. There may also be regimen issues, including tolerability or toxicity issues involving serious adverse effects.
- However, there are other reasons for insufficient drug levels like a regimen with low potency. Alternatively, the wrong dose may be prescribed or dispensed and even though the patient may be perfectly adherent, this suboptimal dose may be the cause for treatment failure. There might be differences in host genetics that affect drug metabolism. Likewise, there might be issues affecting drug absorption or drug pharmacokinetics and drug-drug interactions.
- Transmitted resistance is another factor affecting the ability to achieve undetectable viral load. If the patient is infected with an NNRTI-resistant virus, for example, any level of efavirenz will be insufficient. This results in viral replication in the presence of the drug and may lead to emergence of further drug resistance even to other classes of drugs. A resistant virus but treatment failure would still occur.

Drastic Decline in HIV Drug Resistance



Harrigan et al CROI 2008

- Between 1996 and 2007 there has been a significant decline in the incidence of HIV drug resistance in the province of British Columbia. Most likely due the advent of better treatments, with lower toxicities profile and pill burden , which has favoured better adherence
- Resistance is still prevalent to Lamivudine and NNRTI's (Efavirenz), and less frequent to PI's drugs.

Conclusions

- Recent evidence supports early initiation of ARV's
- Strategic use of ARV's can improve tolerability, adherence and provide durable and potent viral suppression.
- Frequent monitoring in early treatment allows for early detection of tolerability challenges and viral failure
- Refer patients to HIV specialist when proven viral failure or toxicities