When and What to Start With?

Dr. Silvia Guillemi

BC Centre for Excellence in HIV/AIDS
UBC Clinical Associate Professor
Objectives

- When to start ARV’s
- What to start with
- Monitoring of patient on ARV’s
- Treatment failure
• 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 seroconversion 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 bellow 200 cell/ml patients become increasingly at risk for acquiring opportunistic infections or other AIDS related events and eventually death.
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.
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.
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.
**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.
In a cohort of 17,517 asymptomatic HIV-infected persons, initiating HAART at a CD4 cell count greater than 500/µL decreased mortality by 94%.

Initiating HAART at a CD4 cell count between 351 and 500/µL decreased mortality by 69%, although the numbers of deaths were low in both groups. The majority of deaths were from non-AIDS conditions.

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.

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/mm$^3$) or deferred initiation (until CD4+ cell count < 250 cells/mm$^3$).

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.

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/µL have greater morbidity and mortality than those with viral suppression

– Increasing evidence of detrimental effects of uncontrolled viremia at CD4 cell counts > 500/µL
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/μL 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
Present Antiretroviral Guidelines, including the most recent BC CfE, recommend initiation of antiretroviral therapy in all patients 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/µL 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
- Treatment failure
• 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 forth 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
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.
The highlighted antiretroviral agents are the most commonly used fixed combinations drugs.

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

- 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

<table>
<thead>
<tr>
<th>Backbone</th>
<th>Third Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC (Truvada)</td>
<td>EFAVIRENZ (Atripla) or ATAZANAVIR/ritonavir</td>
</tr>
</tbody>
</table>
| Alternative: ABC/3TC (Kivexa) | Alternatives
- Inl: RALTEGRAVIR
- PI: DARUNAVIR /r
- EI: MARAVIROC
- PI: LOPINAVIR /r
- PI: FOSAMPRENAVIR /r |

*Pl mono-therapy and dual therapy strategies not recommended for clinical practice*


- 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.
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.


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.

Tenofivir 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

<table>
<thead>
<tr>
<th>Potential advantages</th>
<th>Potential disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenient, simple dosing</td>
<td>Low genetic barrier to resistance</td>
</tr>
<tr>
<td>Virologic superiority of EFV + 2 NRTIs vs LPV/RTV + 2 NRTIs[^1]</td>
<td>Use EFV with caution in women of childbearing potential</td>
</tr>
<tr>
<td>Durable efficacy[^2,^3]</td>
<td>CNS AEs of EFV may limit use in small number of patients</td>
</tr>
<tr>
<td>Fewer metabolic AEs (dyslipidemia, insulin resistance) than PIs</td>
<td>Some providers avoid EFV in patients with psychiatric illness and substance abuse</td>
</tr>
<tr>
<td>Consistent activity at high pretreatment HIV-1 RNA and low pretreatment CD4[^1,^4]</td>
<td>Potential for rash, hepatotoxicity</td>
</tr>
<tr>
<td>Preserve PI options for future use</td>
<td>Cross-resistance among first-generation agents</td>
</tr>
</tbody>
</table>


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.

• 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

AE, adverse event; ATV, atazanavir; CNS, central nervous system; DRV, darunavir; EFV, efavirenz; LPV, lopinavir; QD, once daily; RTV, ritonavir.
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 drug 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-morbidities 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
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 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/mm³.

Note that failure is defined by two consecutive viral loads >250 c/mL.
## Patient Monitoring

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

- Resistance testing can only be conducted if pVL is ≥250c/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

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

- Poor potency
- Wrong dose
- Poor absorption
- Drug pharmacokinetics
- Transmitted resistance
- Drug interactions

**Insufficient drug level**

**Viral replication in the presence of drug**

**Resistant virus**

**Incomplete adherence**

**Social/personal issues**

**Regimen issues**

**Toxicities**

---

*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.
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