Combination Anti-Retroviral Therapy (CART) - Rationale and Recommendation

M Dinaker

INTRODUCTION

The wide availability of effective, safe and mostly well tolerated combined anti-retroviral therapy (CART) has made HIV a ‘chronic manageable disease’. It has definitely reduced the mortality and overall incidence of AIDS related illness.

The ‘primary goal’ of CART is maximal and durable suppression of the plasma viral load, thereby restoring the immunologic function (by maintaining the CD4 > 350 by frequent monitoring). However, the currently available antiretroviral drugs (ARTs) cannot eradicate the virus because of a pool of ‘latent infected CD4 cells’ with long half life, which establish themselves during the early stage of sero-conversion.

Benefits of CART

- CD4 recruitment and immune reconstitution. (Fig. 1)
- Prevention of opportunistic infections (OIs) and AIDS related malignancies.
- Better quality of life.
- Reduces transmissibility by suppressing viral load. (hence ‘treatment with CART itself is a ‘preventive public health measure’).  
- Prevention of ‘mother-to-child-transmission’.
- Pre- and post-exposure prophylaxis (occupational and non-occupational).
- Decrease non-AIDS, non-infective events (eg: cardiovascular mortality, HIV associated nephropathy).

Currently available ARTs are classified based on site of action

Fig. 1: Effect of CART on CD4 and viral load
(courtesy The Lancet July 3rd 2010)
during the HIV replication cycle. Basically, there are five
different classes and almost 23 different drugs are currently
approved. (Fig.2).

Various aspects of CART
When to start?
Multiple well designed randomized controlled trials have
tried to address this critical issue recognizing the benefits of
early CART versus cost and therapy related adverse events.
Recent trials across the globe in various settings have clearly
shown the benefits of ‘early’ versus ‘deferred’ CART, in
terms of survival, early immunologic restoration, better
drug tolerability and reduction in OIs, especially TB.3,4,5

Current indications for “STARTING” CART are as follows:
- Asymptomatic HIV positive (including pregnant females):
  Initiate treatment at CD4 \( \leq 350 \). (WHO and NACO 2010
guidelines6,7.
- All symptomatic patients irrespective of CD4 count).
- WHO clinical stage 3 and 4 (irrespective of CD4 count).
- “Offer” treatment in HIV positive patients with CD4
  between 350 and 500, especially with those with high
  viral load (>100,000 copies per ml) and rapid disease
  progression, 2nd trimester pregnancy, age > 60 years, HIV
  associated nephropathy, HIV associated cardiomyopathy
  and those with hepatitis B virus co-infection. (IAS-USA
  expert panel).8

Before initiating CART, other non-drug issues need to be
addressed such as:
- Whether patient is ‘ready’ and aware of need for life-long
  therapy.
- Associated psychosocial and economic issues.
- Knowledge about importance of treatment adherence,
  side effects of medications.
- Ensure availability of reliable, affordable and
  uninterrupted supply of quality ARTs.

What to start?
All patients must be started on 3 drug combination from 2
different classes of drugs. 2 NRTIs and one NNRTI comprise
the 1st line CART in most cases. These drugs are currently
available as convenient ‘fixed drug combinations’ (FDCs).
(For those who are HIV serotype 2, NNRTI should not be used
and instead protease inhibitors (Pis) have to be used). The
typical regimens comprise the following:
- Zidovudine (AZT) + Lamuvidine (3TC) + Ezafirenz (EFV).
- AZT + 3TC + Nevirapine (NVP).
- Tenofovir(TDF) + 3TC / Emtricitabine (FTC) + EFV.
- TDF + 3TC + NVP.

Due to disabling/life-threatening and disfiguring
toxicities of STAVUDINE (d4T) such as lactic acidosis,
peripheral neuropathy and lipoatrophy, WHO has
strongly recommended to phase out the drug and replace
with AZT or TDF.

A triple NRTI combination (comprising of AZT + 3TC + abacavir
(ABC) OR AZT + 3TC + TDF) may sometimes be offered
(though ‘weak’) in the following clinical situations when
NNRTI is relatively contraindicated or there is intolerance:
- HIV / TB co-infection in pregnant females.
- Chronic HBV co-infection.
- HIV 2 infection.

CART in HIV / TB co-infection
- Start TB treatment first, followed by CART as soon as
possible. (If CD4 is < 100, start within 2 weeks of initiating anti-TB drugs. If CD4 is > 350, then initiate CART after ‘intensive phase’ of anti-TB treatment is completed.

- Use efavirenz as the preferred NNRTI. (In case of pregnant female with ‘active TB’, a triple NRTI option may be used, as efavirenz should be avoided in first trimester (teratogenic).

- **Watch for the development of IRIS, especially in patients whose CD4 is < 100 at the time of initiation of CART.**

(IRIS or ‘immune reconstitution inflammatory syndrome’ (previously also called ‘paradoxical reaction’, may be simply defined as the occurrence or manifestation of new or existing OI within six weeks to six months after initiating CART; with an increase in CD4 count. (NACO). If severe, may need addition of steroids. There is no need to change the CART)

**CART in HIV / HBV co-infection**

- Start CART in all who need treatment for HBV, irrespective of CD4 count.
- Start with TDF and 3TC / FTC based regimen (as these drugs are active against both the viruses).

**CART: When to “SUBSTITUTE”?**

“Substitution” of “single” drug of CART may be done in the following situations:

- Serious adverse event (SAE) attributable to a specific drug.
- Pregnancy: (substitute EFV with NVP).
- Occurrence of active TB (substitute NVP with EFV).

**CART: When to “SWITCH”? (“Treatment failure”)**

There are three ways of defining ‘treatment failure’:

- **“Virologic failure”:** Failure to achieve undetectable viral load (VL) at the end of week 24 after initiating CART OR viral rebound (>5000 copies/ml) after achieving undetectable levels
- **“Immunologic failure”:** Fall in CD4 count below pre-treatment baseline or 50% fall from peak CD4 while on CART OR CD4 persistently below 100 (at the end of one year of CART).
- **“Clinical failure”:** Occurrence or recurrence of HIV-related events after at least six months of CART (exclude IRIS).

Virologic failure may precede clinical failure by several months to years. Hence, periodic monitoring of at least CD4 count (ideally also viral load) by reliable and affordable laboratory access is essential part of management. Sometimes a phenomenon called ‘CD4 - viral load disconnect’ (limited CD4 reconstitution with maximal virologic suppression) may be observed especially in the following clinical situations:

- Baseline CD4 very low at the time of initiation of CART.
- HCV co-infection on PEG Interferon therapy.
- Intercurrent infections.
- Lymphoma.
- AZT based treatment.

**When to switch?**

The currently recommended algorithm proposed by the WHO may be followed while contemplating a ‘switch’ in CART.

**What to “Switch” to?**

- A boosted protease inhibitor (PI/r) PLUS two NRTIs are
For the boosted PIs, the preferred combination is Atazanavir (ATV) boosted with ritonavir OR Lopinavir (LPV) boosted with ritonavir. (Randomised clinical trials have shown comparable efficacy between the two boosted PI regimens.)

The second line CART as recommended by the IAS-USA panel differs from the WHO recommendation and is as follows:

**3rd line options**: With increasing duration of CART, some patients will require a 3rd line option (expensive), which includes new class of drugs such as ‘integrase inhibitors’ (raltegravir), new NNRTI (ertavirine, which has no cross resistance to other NNRTIs) and 2nd generation PI (Darunavir-boosted). Studies have shown good virologic response in multi-drug experienced patients.

**SOME UNANSWERED QUESTIONS**

- Is the immunodeficiency fully reversible by CART?
- Are the currently available CARTs sufficient to provide lasting viral suppression for decades?
- How cost effective are the newer agents to be accessible on a global public health scale?
- What is the role of persistent inflammation and residual immunodeficiency in the premature onset of cardiovascular disease, renal disease etc?
- Can HIV be cured?

**SUMMARY**

1. As of 2010, the threshold for initiating CART is a CD4...

<table>
<thead>
<tr>
<th>Target population</th>
<th>2010 ART guideline</th>
<th>2006 ART guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+ adults and adolescents</td>
<td>If d4T or AZT used in first-line therapy</td>
<td>TDF + 3TC (or FTC) + ATV/r or LPV/r</td>
</tr>
<tr>
<td></td>
<td>If TDF used in first-line therapy</td>
<td>△AZT+3TC (or FTC) + ATV/r or LPV/r</td>
</tr>
</tbody>
</table>

**Table 1**

**Targeted VL strategy for ‘failure’ and ‘switching’**

1. Suspected clinical / immunologic failure
2. Test viral load
3. VL > 5000 copies/ml
4. Adherence interventions
5. Repeat VL
6. VL < 5000
7. DO NOT SWITCH
8. VL > 5000
9. SWITCH to 2nd line

**WHO 2010**

**Recommended Drugs**
- Tenofovir/emtricitabine
- Abacavir/lamivudine
- Thymidine analogues

**Key 3rd Drug Recommend**
- Efaviren, Atazanavir/r, Darunavir/r, Raltegravir

**Alternative**
- Lopinavir/r, Fosamprenavir/r, Maraviroc
count of 350 or less. In some situations, treatment may be offered at CD4 counts 350 - 500.

2. Early treatment is “preventive”.
3. Follow approved guidelines only.
4. Fixed drug combinations offer convenient, cost effective and low pill burden regimens.

5. Emphasis should be on quality, affordable laboratory tests including CD4 and viral load tests.
6. Identify ‘treatment failure’ EARLY and correct the reasons for the failure.
7. New drugs and new class of drugs hold good promise.

REFERENCES
7. www.naco.org
8. www.nihinfo.gov