CONTROVERSIES IN FIRST-LINE ANTI-RETROVIRAL THERAPY

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Introduction
There is tremendous development in the management of HIV/AIDS patients over the last few years. Many options are available in private sectors but there are limited options in government sector. There are different guidelines to start the anti-retroviral therapy (ART) by the different authorities like CDC, DHSS, WHO etc. Till to date NACO has given guidelines to initiate ART when patient is suffering from opportunistic infections (OI) or CD4 <250. But in Private sector there is a trend to start ART as early as possible.

ART UNDER NACO
Under NACO Program only 5 drugs are available for first line therapy i.e. 3 NRTI (Lamivudine (3TC) (L), Stavudine (d4T) (S), Zidovudine (ZDV) (Z)) and 2 NNRTI (Nevirapine (NVP), (N, Efavirenz (EFV), (E). And only 4 drug combinations can be made i.e. ZLN, SLN, ZLE, and SLE. If patients become resistant to one regime then he is resistant all 4 regimes

How to start ART (as per NACO)
AZT based regime is preferred over d4T because d4T will have more serious long term side effects. However, when Hb% < 8.5 gm then d4T based regime is started. AZT can cause bone marrow depression. 3TC is the least toxic drug and is the part of all the regimes. NVP is added as third drug because 80% supply of NNRTI is the NVP (due to financial constrains). Hence 80% of the patients at ART center are on ZLN/SLN. Efavirenz based regime i.e. ZLE/SLE is used when there is NVP rash (severe & not mange by anti-histaminics) or patient is on AKT (Rifampicin based). Rifampicin decreases blood level of nevirapine significantly.

Alternative Primary line under NACO program:
When patients developed anemia due to AZT and Peripheral Neuropathy or lactic acidosis due D4T or patient has Hepatitis B co-infections then AZT and d4T is replaced by Tenofovir. When patient gets severe Skin sash or Steven Johnson syndrome due to NVP and EFV or Ataxia or psychiatric manifestations due to EFV or patient has HIV-2 infections then Protease inhibitors i.e. Ritonavir boosted lopinavir (LPV/r) is started.

ART IN PRIVATE SECTORS
Plenty of the drugs are available in the market (Table 1). Therefore there is need to think before choosing proper drug combinations.

1. **Cost benefit ratio**: Costly drugs are not always a better option and some costly medications (Raltegravir, darunavir) are very good drugs but not affordable to most of the patients.

2. **Side effect profile of the drugs**: D4T is very cheap & good drug as an efficacy but has severe & sometimes life-threatening side effects. Hence d4T is hardly being used in developed nations.

3. **Possible drug resistance pattern & their benefit**: Mutations are not always a bad for the patients. Sometimes it benefits the patients e.g. M184V is the resistance to 3TC but it weakens the


virus which can be killed by other drug easily.

4. **Concomitant other therapies:** If patient is on Rifampicin then NVP or PI cannot be given. Avoid TDF with DDI as it causes drop in CD4 cells.

5. **Suitable dosing:** Compliance will be very good (95%) if patient is on once or twice a day.

6. **Underlying other diseases:** In patients of Hepatitis B co-infections ART drugs should be used judiciously. If treatment is required for both conditions (HIV and Hepatitis B) then TDF + 3TC is preferred.

7. **Abnormal hematological & biochemical parameters:**
   - If Hb% is <8.5 then AZT is not used or s. creatinine value is more than normal then TDF is contraindicated and dose of NRTI has to be adjusted.

**Choosing the drugs for the first line ART:**

3TC/FTC remains the main stay of ART in government or private sector because it is safe, cheap and once a day dosing. It also results in early M184V mutation which makes the virus weak and easily killed by other drugs. TDF is the second drug of choice because it is relatively cheap and it has fewer side effects with a once a day dosing. Over a few years it may results in K65R mutations in virological failure patients.

K65R mutation causes hypersensitive to AZT and d4T as it may prevent TAMs and TAMs may prevent K65R mutations. Thus Tenofovir in first line ART potentiates the effects of AZT & vice-a-versa. But tenofovir scores over AZT for first line ART as per Table 2. K65R mutation gives partial or full susceptibility to Abacavir & DDI.

Efavirenz is preferred as a third drug because it has less side effects, once a day dosing, relatively cheap, as effective as Protease inhibitors and preserved PI for 2nd line. It is also a preferred drug with concomitant AKT (Rifampicin based). Hence preferred Triple Drug combination is 3TC or FTC, TDF and Efavirenz. It is available as single pill at reasonable cost and preferred over all other drugs and all over world in treatment Naïve patients.

**Drug switch/ dose adjustment**

If patient has kidney failure then TDF is replaced by AZT or ABC. Dose of 3TC, AZT or ABC has to be adjusted according to creatinine clearance. Adjustment in dosing of NNRTI is not required. Before starting ABC, HLA 5701* is advised to avoid life threatening hypersensitivity reaction. PI may be initiated in a treatment naïve patient as per alternative Primary line under NACO program. Any PI may be used however almost all PI has to be boosted by Ritonavir.

**PI Based Regime in first line ART**

ATV/r is preferred due to low cost, single daily dosing, single pill containing Ateznavir and Ritonavir and with least side effects. Patients may get hyperbilirubinemia without any liver damage and there is no need a change in medications. Lopinavir/r may be other alternative but ATV/r scores over LPV/r as per Table 3. However any PI can be used. Recently Darunavir is considered better PI due to its resistance profile but it is costly medicine. Tipranavir is avoided due to its CNS side effects.

**Other newer drugs in first line regime**

a. **Raltegravir (Integrase inhibitor):** It may be used as a first line ART drug when cost is not the problem. It is very effective & least toxic drug. It has rapid and potent antiretroviral activity, which was non-inferior to that of

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**Table 1: Available ART drugs in the market**

<table>
<thead>
<tr>
<th>NRTI/ NNRTI</th>
<th>Protease inhibitors</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>ABC</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>DDI</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>FTC</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>3TC</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>D4T</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>ZDV</td>
<td></td>
</tr>
<tr>
<td>NNRTI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>DLV</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>EFV</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>NVP</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td></td>
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</tr>
</tbody>
</table>

**Table 2: Showing comparison between AZT & TDF**

<table>
<thead>
<tr>
<th>Side effect</th>
<th>AZT</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for Change of the drug</td>
<td>Yes (Anemia, GI intolerance)</td>
<td>Yes (Kidney failure)</td>
</tr>
<tr>
<td>Dose</td>
<td>twice a day</td>
<td>once a day</td>
</tr>
<tr>
<td>TAMS Resistant to AZT, prevents K65R mutations</td>
<td>Sensitive</td>
<td></td>
</tr>
<tr>
<td>K65R Avoid TAMs</td>
<td>Still it may work</td>
<td></td>
</tr>
<tr>
<td>Cost inclusive of 3TC/FTC (MRP)</td>
<td>Rs.1300-1400 PM</td>
<td>Rs. 1200-1300 PM</td>
</tr>
</tbody>
</table>

**Table 3: Showing comparison between ATV/r & LPV/r**

<table>
<thead>
<tr>
<th>ATV/r</th>
<th>LPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1 Tablet a day</td>
</tr>
<tr>
<td>Cost (MRP)</td>
<td>Rs. 3000/- PM</td>
</tr>
<tr>
<td>Side effects</td>
<td>Lipid abnormality, drug interaction, hyperbilirubinemia (reversible)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Less</td>
</tr>
<tr>
<td>Resistance profile</td>
<td>SAME</td>
</tr>
</tbody>
</table>

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efavirenz at week 48. Raltegravir is a well tolerated alternative to efavirenz as part of a combination regimen against HIV-1 in treatment-naive patients.5

b. Maraviroc (CCR -5 antagonists): It has few clinical trials in treatment Naïve patients. It also needs CCR-5 tropism test which is available at very few centers and it is costly. This drug is not used in first line regime because better alternatives (efavirenz, atazanavir/r, darunavir/r, raltegravir) are available.6

c. Enfuvirtide (Entry inhibitor): It is available as only injectable drug and it is to be administered twice a day. Patients get swelling at the site of injection. And it is too costly affair for first line ART

d. Etravarine (NNRTI): It is useful drug after K103N mutation. Hence this drug is used in 2nd line regime i.e. after resistance to NVP/EFV.

Genotyping:

Ideally Genotyping is needed in every patient including treatment naïve patients. But due to cost factors it is usually advised in virological failure patients. Genotyping report may be subjected resistance testing on web site (http://hiv-4.stanford.edu)

Conclusion

There is a little choice in government program but in Private sectors there are n numbers of options. But 2 regimes are preferred as first line ART because these are relatively cheap with least side effects and good dosing schedule.

1. 3TC or FTC, TDF and EFV as a single tablet at bed time
2. TDF + 3TC or FTC and ATV/r (When there are side effects of NNRTI) 2 tablets OD

However DHHS guidelines- 2009 for starting First line ART is as follows:7
1. ART for Asymptomatic patients with CD4 counts ≤ 500 cells/mm3
2. The four “preferred” regimens for treatment-naive patients-
   a. EFV/TDF/FTC
   b. ATV/r+ TDF/FTC
   c. DRV/r+ TDF/FTC
   d. Raltegravir + TDF/FTC

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7. JW AIDS Clin care April 17, 2009