Evolution of Anti- Retroviral Therapy: Multiple Pills to Fixed Drug Combinations

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Introduction

First anti-retroviral drug available for the treatment of HIV/AIDS patients was Zidovudine (AZT) in 1986. AZT monotherapy was the only available ART and it resulted in early resistance to AZT. Hence there was a need for new antiretroviral drugs to treat HIV/AIDS. With a rapid development in research many new drugs came in the market. At present more than 25 antiretroviral drugs are available for the treatment of HIV/AIDS. With advancement in research and availability of RCTs results, it is evident that triple drug therapies are the only option for the treatment of HIV/AIDS to avoid early resistance. With the availability of newer and better drugs, older drugs like zalcitabine, delavirdine, stavudine were discarded. Older protease inhibitors (PIs) like indinavir, saquinavir are also being used less frequently due to availability of better PIs.

Combination Therapy

Triple drug therapy was tried in 1993 by Ann C. Collier in clinical trial for the first time. Zidovudine, zalcitabine and Saquinavir were administered to 302 patients and followed up to 1 year. There was viral suppression in 96% of patients but there were many adverse reactions. Zalcitabine was hardly used in India due to availability of better drugs. First FDC available in the market was ZL (AZT, Z + lamivudine (3TC, L) in the year 2000. Third drug available at that time was saquinavir soft gel capsule (100 mg) and dose was 600 mg TDS i.e. 6 capsule 3 times a day. Hence patient had to take 18 capsule saquinavir, 3 tablets AZT (200 mg, TDS), 2 tablets of 3TC (150 mg BD) and 1 tablet each of Septran DS and fluconazole as a prophylaxis. Pill burden for patients was 25 pills/day. Hence compliance was a major issue. Saquinavir formed clumps if exposed to heat, hence lot of these costly medicines were wasted.

Era of FDC

Around year 2000 many drugs like stavudine (S), nevirapine (N), efavirenz(E) were available in market. Drugs like AZT, d4T, 3TC and NVP have twice a day dosing. Indian pharmaceutical companies were pioneer in combining these drugs and prepare FDC of SLN and ZLN as a single pill at an affordable cost. ZLN or SLN dose was 1 tablet twice a day. Due to side effects of AZT, SLN was most preferred regime at that time. This improved compliance and therefore many patients were put on this regime. Morbidity and mortality in HIV/AIDS patients started reducing. With the introduction of ZLN/SLN combination many lives were saved in India and African countries. Indian pharmaceutical companies must get credit for this initiative.

Adverse Reactions of d4T

Over the time d4T was found to have many long-term serious adverse reactions like lactic acidosis, sensory motor neuropathy, pancreatitis, severe disfiguring lipodystrophy and metabolic complications like abnormal lipid profile. Lipodystrophy itself became taboo of the disease hence d4T was withdrawn from Western and developed countries from year 2005. Newer and better drugs like abacavir (ABC) and tenofovir (TDF) were introduced to replace d4T. Around 2010 WHO also advised to stop use of d4T and in 2013 NACO stopped using d4T. At present only in a few selected conditions d4T is used, if patient’s hemoglobin is less than 9.5 gm%, raised creatinine and HLA B5701 positive. Other alternatives for d4T, like raltegravir or PIs, are available but cost prevents their use.

Era of Single Pill a Day

Subsequently FDC of TDF + 3TC, TDF + FTC (emtricitabine), ABC+ 3TC were available as dual therapy and FDC of TDF + 3TC + EFV (TLE), TDF + FTC + EFV (TEE) were available as triple drug combination therapy. In addition,
ZLN and ZLE are also available in the market as well as in government program. WHO in 2013 advised TLE or TEE as a first-line regime to all treatment naïve patients unless it is contraindicated. NACO in very next year adopted same policy and all treatment naïve were started on TLE regime. EFV has a few central nervous system adverse effects for initial few days in 14-50% of the patients. Adverse effects include dizziness, sedation and ataxia which settle down in few days. Various studies showed renal involvement with TDF (1-10%) and osteoporosis (2-4.5%).

There are good reasons to use TLE or TEE as a first-line therapy. This regime is well tolerated and dose is once a day single pill at bedtime with least side effects that enhance the compliance. Virological failure on TLE or TEE regime leads to K65R, M184V and K103N mutations. M184V mutation increases susceptibility to AZT. With K65R mutation, Thymidine associated mutations (TAMs) can be prevented. Hence mutant virus is hypersensitive to AZT. If AZT is used for first-line ART then there are multiple TAMs on failing regimes and with multiple TAMs efficacy of TDF and ABC is compromised. Use of TLE or TEE regime in first-line saves AZT for second-line regime.

Other Single Pill FDCs

There are other single pill FDCs available in the US and some other developed countries but at present these FDCs are not available in India, these include Rilpivirine + Tenofovir + Emtricitabine; Elvitegravir (EVG) + Cobicistat (COBI) + Tenofovir + Emtricitabine and Dolutegravir (DTG) + Abacavir + Lamivudine.

Rilpivirine proved virologically noninferior to efavirenz through 96 weeks when either nonnucleoside was combined with tenofovir/ emtricitabine in the ECHO and THRIVE studies, but in the study there was 22.1% virologic failure rate in the rilpivirine arm versus 11.7% virologic failure rate in the efavirenz arm. Resistance analysis showed virologic failure rates after 1 year of follow-up were 11.5% in the rilpivirine arm and 4.2% in the efavirenz arm. In the second year of follow-up, rates of additional virologic failure were low with both rilpivirine (2.7%) and efavirenz (2.6%). Hence rilpivirine, tenofovir and emtricitabine combination is not superior to TEE combination, rather it is less effective and will have more chances of resistance. Although it works with K103N mutations but efficacy is compromised. Hence this regimen is useful in treatment naive patient but efficacy is compromised in NVP/EVF-experienced patients.

Treatment with EVG/COBI/FTC/ TDF was associated with more rapid achievement of HIV-1 RNA less than 50 copies/ml than EVF/ FTC/TDF (P < 0.05 at weeks 2, 4, 24). Plasma HIV-1 RNA less than 50 copies/ml at week 24 were 90% (43/48) in the EVG/COBI/FTC/TDF group and 83% (19/23) in the EVF/ FTC/TDF group.

A total of 833 participants received at least one dose of study drug at DTG–ABC–3TC versus EVF–TDF–FTC in randomized, double-blind, phase 3 study. At week 48, the proportion of participants with an HIV-1 RNA level of less than 50 copies per milliliter was significantly higher in the DTG–ABC–3TC group than in the EVF–TDF–FTC group (88% vs. 81%, P=0.003), thus meeting the criterion for superiority. The DTG– ABC–3TC group had a shorter median time to viral suppression than did the EVF–TDF–FTC group (26 vs. 84 days, P<0.001), as well as greater increases in CD4+ T-cell count (267 vs. 208/µL, P<0.001). The proportion of participants who discontinued therapy owing to adverse events was lower in the DTG–ABC–3TC group than in the EVF–TDF–FTC group (2% vs. 10%); rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) were significantly more common in the EVF–TDF–FTC group, whereas insomnia was reported more frequently in the DTG–ABC–3TC group. No participants in the DTG– ABC–3TC group had detectable antiviral resistance. Dolutegravir plus abacavir–lamivudine had a better safety profile and was more effective through 48 weeks than the regimen with efavirenz–tenofovir DF–emtricitabine.

In another study, it was shown that 20% of patients did not respond to therapy and had detectable levels of plasma HIV-1 RNA, perhaps due to non-adherence, but also did not harbor any detectable drug resistance mutations. Moreover, M184V mutation, associated with resistance to lamivudine and emtricitabine, has been present in some cases of failure involving boosted PIs but has not been detected in any cases of viral rebound following first-line dolutegravir. Virological failure is rare with DTG. It may be due to virus becoming replication-incapacitated after resistance to dolutegravir. Hence, such variants do not expand enough to be detectable in patient plasma.

Dolutegravir + Abacavir + Lamivudine regime is most challenging and efficacious regime in the present scenario and may be future first-line ART regime. Patient on ABC may develop severe hypersensitivity to ABC and may cause death. Hence HLA B 5701 test has to be carried out to know the hypersensitivity to ABC. If HLA B 5701 detected then ABC is contraindicated.

Conclusion

Single pill a day is the need for treatment of HIV/AIDS patients as the treatment is lifelong. Although only TLE or TEE is available as a single pill in most of the countries, other three good single pill regimes are available in developed nations.
Dolutegravir (DTG) + Abacavir + Lamivudine regime is most promising regime and may be future preferred single pill regimes all over the world.

**Abbreviations**

1. Anti- Retroviral Therapy = ART; 1a. Fixed Drug Combinations = FDCs; 2. Zidovudine = AZT (Z); 2a. Randomized control trials = RCTs; 3. Lamivudine = 3TC (L); 3a. Stavudine = d4T (S); 4. Protease inhibitors = PIs; 4a. Stavudine = d4T (S); 5a. Efavirenz = EFV; 6. Emtricitabine = FTC (E); 6a. Zidovudine = AZT (Z); 5. Nevirapine = NVP (N); 7. Elvitegravir = EVG); 7a. Thymidine associated mutations = TAMs. 8. National Aids Control organization = NACO; 7a. Thymidine associated mutations = TAMs.

**References**