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# How ART Guidelines are Changing Over the Years

*BB Rewari*, Vipin Mediratta***

## Introduction

Antiretroviral therapy (ART) is seen as a panacea for People Living, with HIV (PLHIV) and has helped save millions of lives in addition to improving quality of life. In addition, this has saved many countries from catastrophic economic consequences of the disease.

Zidovudine, being used for some malignancies, was the first drug shown to be effective against HIV in 1985. Soon it was felt that the virus developed resistance quickly and the drug becomes in effective in less than a year with Zidovudine monotherapy. By 1995, many studies had demonstrated the clinical benefits of using a two-drug combination of Zidovudine or Stavudine in combination with Lamivudine. The year 1996 was a landmark year in the ART journey when results of using a triple drug combination using protease inhibitors were revealed at the International AIDS Society (IAS) conference in Vancouver. These drugs over the years have transformed lives of millions of people and have changed the outlook of HIV from that of a virtual death sentence to a chronic manageable condition. Fig. 1 shows the development of various anti-retroviral (ARV) drugs the over last three decades.

Besides treating those with HIV, ARV drugs are also used for preventing mother to child transmission of HIV (PMTCT), for preventing acquiring HIV infection in case of accidental exposure to the virus (Post-Exposure Prophylaxis, PEP) and for preventing HIV infection in HIV negative individuals with substantial risk of being infected (Pre-exposure prophylaxis, PrEP).

## What are the options available for ART

Highly Active Antiretroviral Therapy (HAART) or simply ART is a combination of three ARV drugs from different groups in a fixed dose combination (FDC). The "one pill a day" therapy has potential for good adherence as ART is a lifelong therapy. Production of generic formulations of these drugs have helped reduced its costs from USD 10,000 to less than USD 80 now, making it affordable for most people. In addition, roll out of free ART programme in countries has helped increase coverage of ART, resulting in individual patient benefits, as well as prevention of transmission of HIV due to reduction in viral load. Presently available ARV drugs cannot cure HIV as the virus remains dormant in resting state in some cells like spleen, brain, bone marrow, etc. It starts replicating again if the ART is stopped. Hence, ART is a lifelong therapy.

The ARV drugs broadly act at various steps in the life cycle of the virus, either by blocking enzymes (reverse transcriptase, protease, integrase) needed for replication or by blocking entry of HIV into CD4 cells (Fusion inhibitors) or by blocking maturation of virions and their budding out from CD4 cells. Based on the site of action, these drugs are broadly divided into six classes (Table I).

The combinations of antiretroviral drugs inhibit the replication of HIV leading to slowing of disease progression while reduced CD4 cell destruction leads to better immunity and fewer opportunistic infections. Over the years, the drugs have been evolving towards better efficacy, fewer toxicities, better pharmacokinetics, fewer drug-drug interactions and lesser chances of resistance. This has led to optimisation of ART and WHO has released updated ART guidelines in July 2019.

In the early days, when HAART was just being introduced, it was considered that a 'hit hard, hit early' would be adopted. However, evidence that emerged in those years questioned the advantages of early HAART. Till about three years ago, treatment for HIV-infected person was based largely on the CD4 count levels and clinical stage of the infection. The CD4 count cut-off point for ART initiation was less than 200 cells/cmm in 2004 and later moved to less than 350 cells/cmm in 2010. The cut-off was advanced to less than 500 cells/cmm in 2013 while in 2016, the recommendation came to Treat All, regardless of clinical stage or CD4 count. Fig. 2 summarises the changes in CD4 cut-off for ART initiation over the years.

**Ex-Associate Professor, **Associate Professor, Department of Medicine, PGIMER, Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*

*Corresponding Author: Dr BB Rewari, Ex-Associate Professor, Department of Medicine, PGIMER, Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 9811267610, E-mail: bbrewari@hotmail.com.*

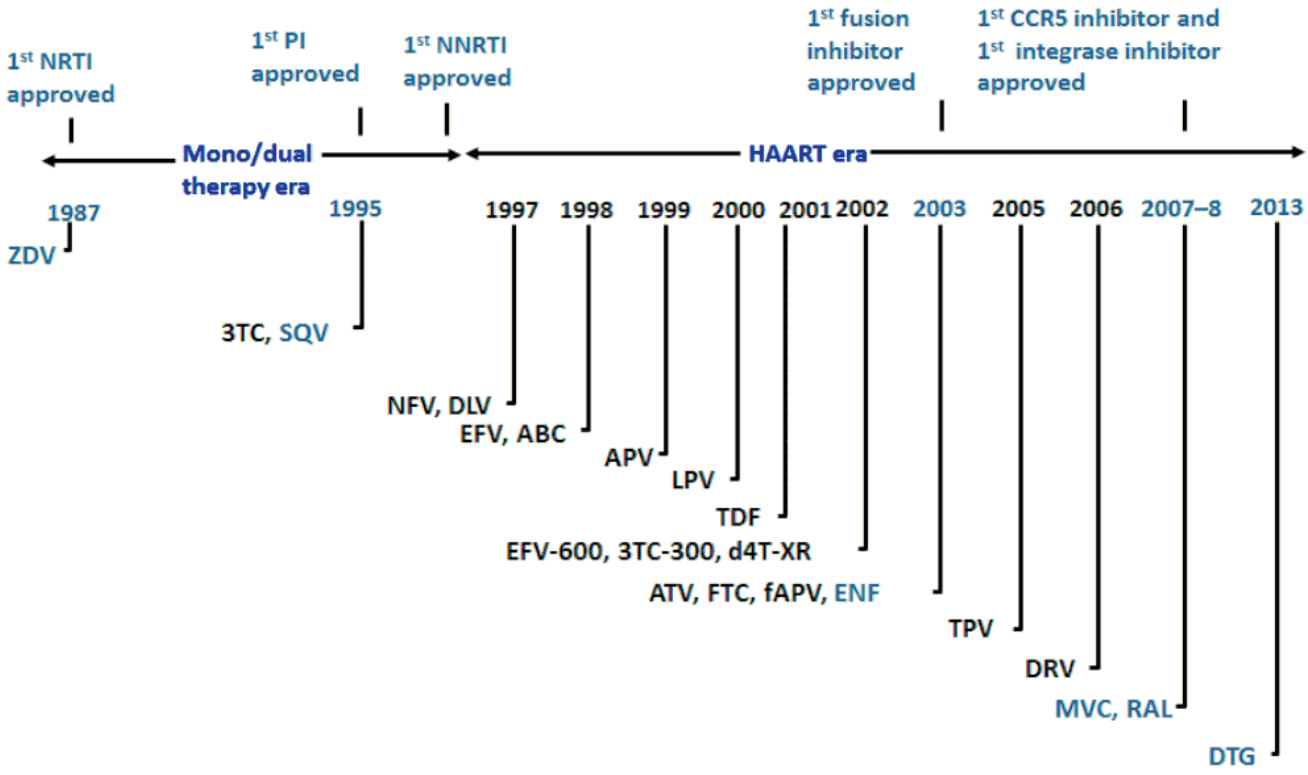


***Fig. 1:*** *Evolution of ARV therapy.*

**Table I: Classes of ARV drugs currently in use.**

| Category | Drugs | |
|---|---|---|
| Nucleoside reverse Transcriptase inhibitors (NsRTI) | Zidovudine (AZT/ZDV)<br>Abacavir (ABC) | Lamivudine (3TC)<br>Emtricitabine (FTC) |
| Nucleotide reverse Transcriptase inhibitors (NtRTI) | Tenofovir (TDF) | |
| Non-nucleoside reverse transcriptase inhibitors (NNRTI) | Nevirapine (NVP)<br>Etravirine | Efavirenz (EFV) |
| Protease inhibitors (PI) | Ritonavir (RTV)<br><br>Tipranavir (TPV) | Lopinavir (LPV)<br>Atazanavir (ATV)<br>Darunavir (DRV) |
| Integrase inhibitors | Raltegravir (RGV) | Dolutegravir (DTG) |
| CCR5 entry inhibitor | Maraviroc | |

## When to start ART is no longer a question or discussion point

The basis for these changes has been evolving evidence from various randomised clinical trials and large observational cohorts which have revealed that with earlier ART initiation, there was a significant delay in progression to AIDS and reduction in incidence of TB. These studies are briefly summarised in Fig. 3.


***Fig. 2:*** *Evolution of CD4 cut-offs for ART initiation over time.*

Hence the current recommendation (since 2016) is to initiate ART for all those who present with HIV infection, regardless of CD 4 count or WHO clinical staging.

## What is the latest WHO recommendation on which drugs to start in ART ?

As described earlier, ART comprises of using at least three drugs from two different groups of ARV drugs in a combination, preferably in a single pill, to improve

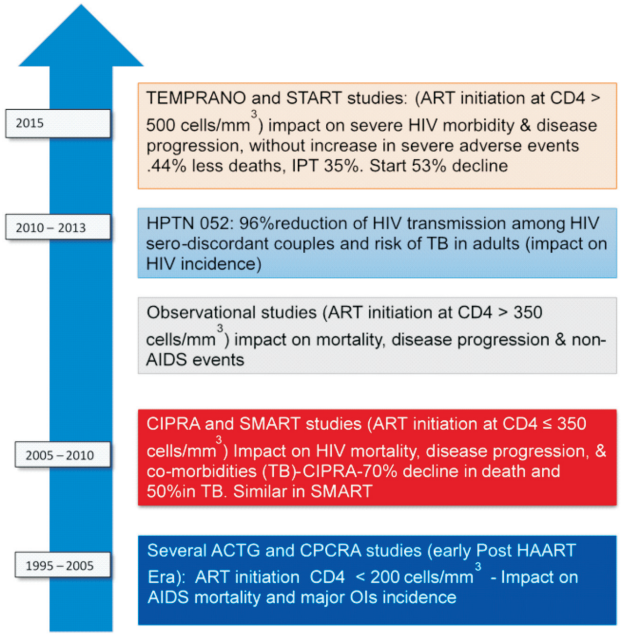


***Fig. 3:*** *Overview and timelines of 'when to start ART' studies.*

adherence to therapy. The most commonly used combination is using two drugs from NRTI and one from NNRTI. So far, most developing countries are currently following a combination of Tenofovir (TDF 300 mg) + Lamivudine (3TC 300 mg) + Efavirenz (EFV 600 mg) in a single pill, as standard of care. This regimen is widely available as a single, once-daily Fixed Dose Combination (FDC) tablet making it easy to prescribe and easy for patients to take thereby facilitating treatment adherence. This regimen has the advantage of harmonisation of treatment for all adults, adolescents, and those with HIV-TB, and HIV-Hepatitis B co-infections, and is also safe in pregnancy.

## So, what has changed in 2018/2019 ?

In the 2018 ART update, WHO recommended use of Dolutegravir (DTG) in first-line ART, based on evidence that with DTG, 1) viral suppression is faster than with EFV (Avg. 4 weeks for DTG vs 12 weeks for EFV), 2) DTG has fewer side-effects, 3) fewer drug-drug interactions, and 4) patients on DTG have a higher threshold for developing resistance.

The SINGLE study compared the efficacy and safety of DTG as compared to current standard of care (Tenofovir plus lamivudine plus efavirenz). A total of 833 participants who had an HIV-1 RNA level of > 1,000 copies/ml were chosen and randomly assigned to DTG-ABC-3TC group or EFV-TDF-FTC group. Primary end-point was the proportion of participants with an HIV-1 RNA level of < 50 copies per ml at week 48 and secondary end-points included the time to viral suppression, change from baseline in CD4+ T-cell count, safety, and viral resistance.

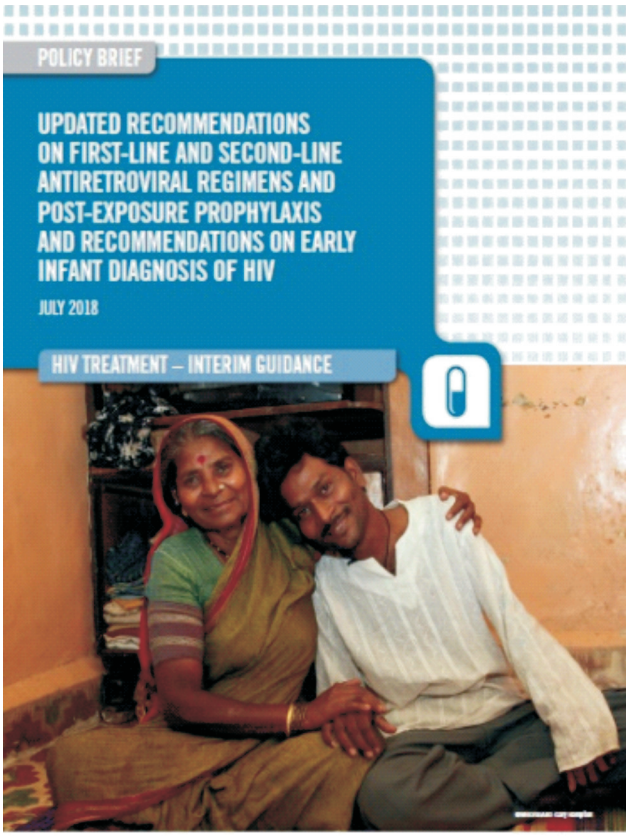


***Fig. 4:***

The key findings from study revealed that at week 48, the proportion of participants with an HIV-1 RNA level < 50 copies per ml was significantly higher in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (88% vs 81%, P = 0.003). It was also seen that DTG-ABC-3TC group had a shorter median time to viral suppression than EFV-TDF-FTC group (28 vs 84 days, P < 0.001), as well as greater increases in CD4+ T-cell count (267 vs 208 per cubic ml, 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 EFV-TDF-FTC group (2% vs 10%).

The results from some other studies like FLAMINGO, SPRING2 and SAILING showed that:-

- DTG achieves viral suppression much faster than EFV (Avg. 4 weeks for DTG vs 12 weeks for EFV).
- There are very few discontinuations on DTG regimen due to drug toxicity (<2%), less than with DRV/r and EFV.
- Main clinical adverse events seen are rash (2% vs 13%)

and neuropsychiatric events (including dizziness). These were significantly more common with EFV (5% vs 35%), while insomnia was reported more frequent in DTG (13% vs 7%) (SINGLE study).

- DTG has a strong resistance barrier. No known treatment-emergent resistance were seen across trials. This was a very significant finding as it is well known that EFV has a very weak genetic barrier to resistance.

Accordingly, the WHO guidelines on what to start were updated in 2018 to include DTG as preferred first-line drug along with Tenofovir and lamivudine. However, an ongoing observational Tsepamo study in Botswana identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. Interim analysis identified 4 neural tube defects out of 426 women taking DTG at the time of conception, for a rate of 0.9% (0.37% - 2.4%). So, 2018 guidelines specified that women and adolescents of child bearing potential who want to become pregnant and have no effective contraception should not use DTG. An EFV-based regimen is a safe and effective first-line regimen and can be used among women of childbearing potential during the period of potential risk for developing neural tube defects (NTDs). However, DTG has been found to be effective for pregnant women and is found in breast milk, resulting in significant plasma concentration in infants and thus a potential important tool to reduce the mother-to-child transmission of HIV infection.

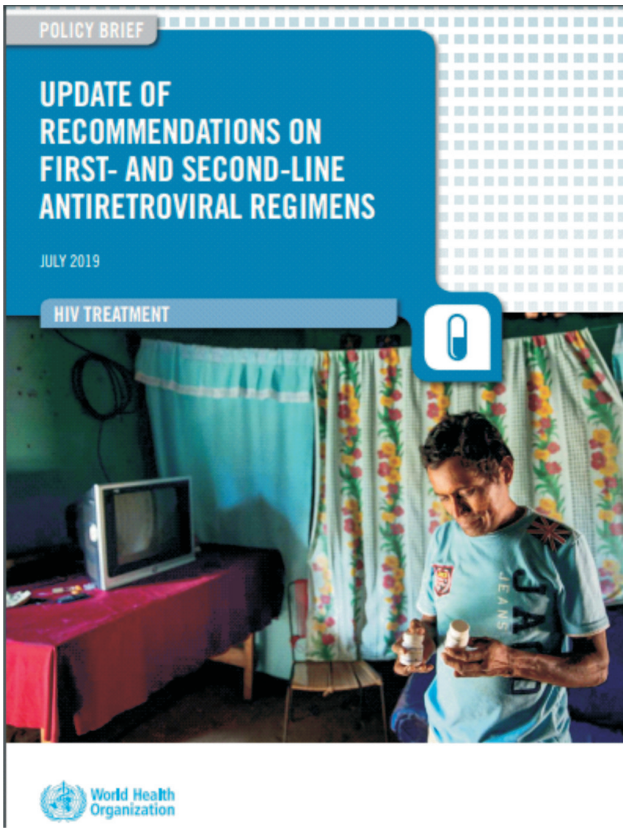


*Fig. 5:*

As new evidences from the Tsepamo study became available, it showed that the risk of NTDs associated with use of DTG at the time of conception is less than originally signaled. The updated prevalence in the study has declined from 0.94% to 0.30%. The difference remains statistically significant compared to EFV, but the overall risk remains low. The risk – benefit models suggest that the benefits of DTG for women of childbearing potential (WCP) newly initiating ART, are likely to outweigh the risks. DTG is also predicted to be more cost-effective, resulting in more disability-adjusted life-years averted at a lower cost than EFV.

The ART guidelines released by WHO in July 2019 recommend that FDC of Tenofovir, Lamivudine and Dolutegravir (TLD) as the preferred first-line regimen for all adults, including women, and upgraded the recommendation from 'conditional' to 'strong'.

It also recommended the adoption of a woman-centered approach to health care, that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect womens autonomy in decision-making and provide information and options to enable women to make informed choices". Table II and III below summarise the WHO 2019 ART guidelines.

**Table II: WHO ART initiation guidelines (July 2019).**

| 2019 WHO guidelines preferred and alternative 1L regimens for adults and adolescents | | |
|---|---|---|
| **Preferred 1L regimen** | **Alternative 1L regimen** | **Special circumstances** |
| TDF + 3TC (or FTC) + DTG* | TDF + 3TC + EFV 400 mg[b] | TDF +3TC (or FTC) +EFV 600 mg[b] |
| | | AZT + 3TC + EFV 600 mg[b] |
| | | TDF + 3TC (or FTC) + pI/r |
| | | TDF + 3TC (or FTC) + RAL |
| | | TAF[c] + 3TC (or FTC) + DTG[a] |
| | | ABC + 3TC +DTG[a] |

**Table III: WHO ART guidelines for those with failure to First-line ART (July 2019).**

| Population | First-line regimens | Preferred Second-line regimens | Alternate Second-line regimens |
|---|---|---|---|
| Adults (≥ 30 kg) | 2 NRTIs* + DTG | 2 NRTIs* + ATV/r or PLV/r | 1 - 2 NRTIs* + DRV/r |
| | 2 NRTIs* + EFV | 2 NRTIs* + DTG | 1 - 2 NRTIs* + DTG |

| Topic | 2002 | 2003 | 2006 | 2010 | 2013 | 2016 | 2018 - 2019 |
|---|---|---|---|---|---|---|---|
| Earlier initiation When to start | CD4 ≤ 200 | CD4 ≤ 200 | CD4 ≤ 200<br>- Consider 350<br>- CD4 d™ 350 for TB | CD4 ≤ 350<br>- Regardless CD4 for TB and HBV | CD4 ≤ 500<br>- Regardless CD4 for TB, HBV PW and SDC<br>- CD4 ≤ 350 as priority | Towards treatment initiation at any CD4 cell count or clinical stage | Towards treatment initiation at any CD4 cell count or clinical stage |
| Simpler treatment 1st-Line ART | 8 options<br>- AZT preferred | 4 options<br>- AZT preferred | 8 options<br>- AZT or TDF preferred<br>- d4T dose reduction | 6 options and FDCs<br>- AZT or TDF preferred<br>- d4T phase out | 1 preferred option and FDCs<br>- TDF and EFV preferred across all pops | Continue with FDC and phased introduction of new options (DTG, $EFV_{400}$) | Two NRTI+ DTG as preferred first-line ART for all adults and women (with informed choice to women of child bearing age |
| Less toxic, more robust regimens 2nd-Line ART | Boosted and non-boosted PIs | Boosted PIs<br>- IDV/r LPV/r, SQV/r | Boosted PI<br>- ATV/r,DRV/r, FPV/r LPV/r, SQV/r | Boosted PI<br>- Heat stable FDC: ATV/r, LPV/r | Boosted PIs<br>- Heat stable FDC: ATV/r, LPV/r | Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens) | Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens) |
| 3rd-Line ART | None | None | None | DRV/r, RAL, ETV | DRV/r, RAL, ETV | Encourage HIV DR to guide | Encourage HIV DR to guide |
| Viral Load Better and simpler monitoring | No | No (Desirable) | Yes (Tertiary centers) | Yes (Phase in approach) | Yes (preferred for monitoring, use of PoC, DBS) | Support for scale up of VL using all technologies | VL at 6 months, 12 months and then every 12 months |

## Conclusion

ART has been evolving rapidly towards earlier initiation with more robust and less toxic regimens. Fig. 4 summarises this evolution. It will continue to evolve. Recently the US FDA has approved a two-drug therapy using only Dolutegravir and Lamivudine and many new drugs are under trial, including once a month injectable options. Simultaneously, a lot of research is ongoing on finding a cure for HIV. Vaccine trials have been partially successful, but the best vaccine available is prevention and, for those infected, early diagnosis and linkage to treatment remains crucial.

In India, ART is available free of cost through 530 government-run ART centres across the country, wherein 1.2 million PLHIV are currently receiving free ART. Yet, there are some who would prefer to access ART from the private sector. Private sector physicians must offer ART according to the treatment and related guidelines adopted in the country, to those who can afford it and also committed to treatment adherence and periodic follow-up. Being a lifelong therapy, adherence and affordability are the two key issues. Hence it is important for clinicians in the private sector to carefully consider these factors before ART initiation. In situations where affordability and adherence are in doubt, clinicians may refer the PLHIV to government ART centre.

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