



Current Antiretroviral Therapies and Future Trends in Management of Human Immunodeficiency Virus-1 Infection

INVITED
REVIEW

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ABSTRACT

Earlier initiation of antiretroviral therapy (ART) for human immunodeficiency virus (HIV)-1 infection is associated with reduced HIV-related morbidity and mortality, improved immune recovery, and reduced risk of HIV-1 transmission. Consequently, international guidelines now recommend ART for all HIV-1-infected adults, regardless of CD4 cell count. The shift in guidance has led to concern regarding long-term ART toxicity, and new strategies to limit ART exposure have been proposed. In this review, we will discuss current recommendations for ART and future trends in management including mono- and dual-therapy, new ART formulations, and novel antiretroviral agents.

Keywords: HIV, AIDS, antiretroviral therapy

INTRODUCTION

The human immunodeficiency virus (HIV) is a cytopathic T-cell tropic lentivirus of the family *Retroviridae*. It is the etiologic agent of the acquired immunodeficiency syndrome (AIDS), which if untreated causes progressive impairment of the immune system, susceptibility to infection, cancer, and death in the majority of cases.

The development of highly active antiretroviral therapy (ART) has revolutionized the management of HIV infection; HIV-infected subjects who commence effective ART in a timely fashion may be expected to have a normal life span (1) and are no longer at risk of transmitting the virus sexually (2). In light of studies demonstrating improved immunologic recovery and less severe HIV morbidity with early initiation of ART, major national and international guidelines now recommend ART for all HIV-infected individuals, regardless of CD4 cell count (3–6). The 2013 UNAIDS 90:90:90 ambition highlights the importance of effective ART in the global response to HIV, advocating that the HIV epidemic can be curtailed if 90% of people living with HIV know their status, 90% of those diagnosed receive ART, and 90% of those on treatment achieve virologic suppression.

Antiretroviral agents are not without side effects, and concerns have arisen regarding the long-term toxicity of these agents. Renal, bone, cardiovascular, hepatic, and neurocognitive side effects are all recognized as complications of ART use. In addition, the pill burden and need for daily administration of currently recommended ART regimens impacts tolerability and may influence adherence.

In this article, we will review current guideline recommendations for ART in HIV-1-infected adults and discuss future trends in management including class-sparing treatment strategies, new antiretroviral drug formulations, and the development of novel classes of ART.

PubMed was searched for relevant articles in English, using the terms “HIV” or “AIDS” and “ART.” Abstracts presented at major international conferences were also referenced.

Current Guidelines for ART

The first drug used in the treatment of HIV was azidothymidine (AZT; zidovudine). It was initially developed in 1964 as a potential cancer chemotherapy, but proved ineffective and development was halted. However, in the 1980s AZT was screened as part of a program to identify antiretroviral agents, and was shown to suppress HIV replication *in vitro* through competitive inhibition of the HIV reverse transcriptase. Unfortunately, the use of AZT and other nucleos(t)ide reverse transcriptase inhibitors (NRTIs) as either mono- or dual-therapy led to the rapid development of resistance-associated mutations and subsequent treatment failure. The later discovery of classes of antiretroviral agents acting at different stages of the viral life cycle led to the use of combination therapy. Combination ART (cART) was associated with improved rates of sustained virologic suppression and became the standard of care for the next 30 years.

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There are five classes of antiretroviral in use at present: NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors. Agents which target the viral capsid and maturation process are under investigation. Classically, cART has included two NRTIs together with a third drug from a different therapeutic class: a PI, NNRTI, or more latterly, an INSTI (Table 1). Less frequently, an entry inhibitor may be considered for the third agent.

Both American and European guidelines recommend a combination of emtricitabine (FTC) with tenofovir disoproxil (TDF) or its prodrug tenofovir alafenamide (TAF), as the preferred backbone NRTI combination (4, 5). This combination has the benefit of robust activity against hepatitis B virus (HBV) and is recommended for all co-infected patients. The nephrotoxicity of TDF can be mitigated by the use of its prodrug TAF (7); however, this combination is not recommended for individuals with a creatinine clearance (CrCl) <30 µmol/L. Both TDF and TAF are coformulated as single tablets with FTC, reducing pill burden for HIV-infected subjects. The combination of abacavir (ABC) and lamivudine (3TC) is no longer recommended first line; studies have shown reduced virologic efficacy in comparison to TDF/FTC in individuals with an HIV VL >100,000 copies/mL (ACTG A5202) (8), the use of ABC requires HLAB5701 genetic testing before administration, and concerns persist about the cardiac side effects of ABC. However, ABC/3TC may be considered in combination with the INSTI dolutegravir (DTG) even in subjects with a baseline VL >100,000 copies/mL, and this is considered an acceptable initial combination in the European AIDS Clinical Society (EACS) guidelines (5) (Table 1).

The choice of a third agent depends on patient and viral characteristics. An INSTI is increasingly preferred in national and international guidance due to the improved side effect profile and tolerability of these drugs. However, INSTIs other than DTG have a lower barrier to resistance than the PIs and may not be appropriate for all patients. PIs, primarily darunavir (DRV), together with a pharmacokinetic enhancer (cobicistat [c] or ritonavir [r]), are recommended for HIV-infected individuals with drug-resistant virus and may be considered for those who are poorly adherent to medication.

Drug resistance to DTG has not yet been observed in clinical practice, and DTG has the advantage of being coformulated with ABC/3TC in a single tablet regimen (STR). However, recent concerns have been raised regarding the CNS toxicity of DTG: drug discontinuation due to side effects is more frequent with DTG than the other INSTIs, and DTG use may be associated with insomnia and depression (9).

Bictegravir (BIC) is a novel INSTI with a high barrier to resistance *in vitro*, recently approved for use with TAF/FTC as an STR for initial ART. The combination of BIC/TAF/FTC has similar efficacy to DTG/TAF/FTC and was well tolerated in clinical trials (10).

Doravirine, a novel NNRTI, has also been approved for use within the American guidelines (4). Doravirine was non-inferior to EFV plus 2NRTI (11) and DRV/r plus 2NRTI (12) in terms of virologic efficacy and was associated with a lower incidence of CNS side effects than EFV (11).

Table 1. Preferred and alternative guideline recommendations for first-line ART

	BHIVA ³	EACS ⁵	DHHS ⁴	WHO ⁶
Preferred backbone	TDF/FTC TAF/FTC	TAF/FTC TDF/FTC ABC/3TC*	TAF/FTC	TDF/XTC
Alternative backbone	ABC/3TC		ABC/3TC* TDF/FTC	AZT/XTC
Preferred third agent	ATV/r DRV/r DTG EVG/c RAL RPV*	RPV* DTG RAL EVG/c DRV/c or DRV/r	BIC DTG RAL	EFV
Alternative third agent	EFV	ATV/c or ATV/r	DRV/c or DRV/r ATV/c or ATV/r EFV DOR EVG/c RPV*	DTG EFV (400) NVP

*Use if baseline HIV-1 VL <100,000 copies/mL. BHIVA: British HIV Association; EACS: European AIDS clinical society; DHHS: Department of health and human services; WHO: World health organisation; TDF: Tenofovir disoproxil fumarate; FTC: Emtricitabine; TAF: Tenofovir alafenamide; ABC: Abacavir; 3TC: Lamivudine, XTC, FTC or 3TC, AZT: Zidovudine; ATV: Atazanavir; r: Ritonavir; DRV: Darunavir; DTG: Dolutegravir; EVG: Elvitegravir; c: Cobicistat; RAL: Raltegravir; RPV: Rilpivirine; BIC: Bictegravir; EFV: Efavirenz; DOR: Doravirine; NVP: Nevirapine

In combinations of equivalent virologic efficacy, response to treatment may be determined by tolerability. While three-drug combinations remain extremely effective, a desire to improve the tolerability of ART regimens has promoted interest in the use of mono- and dual-therapy to limit ART exposure.

FUTURE TRENDS in ART

PI monotherapy

Treatment naive

The use of ritonavir(r) boosted PIs as monotherapy in HIV infection has been under investigation since the early 2000s. Data on the use of PI monotherapy as initial ART are unpromising. In the MONARK trial, comparing boosted lopinavir (LPV/r) with AZT/3TC/LPV/r, the use of LPV/r as initial therapy was associated with emergent PI resistance mutations and lower rates of virologic suppression at 48 weeks (13). As a consequence, PI monotherapy cannot be recommended as initial therapy in HIV-1-infected subjects.

Treatment experienced

The use of PI monotherapy as a switch strategy to simplify ART

in virologically suppressed individuals has also been studied, with more encouraging results. Boosted LPV, atazanavir (ATV), and DRV have all been investigated as monotherapy, and the use of PI monotherapy as a switch in virologically suppressed individuals has been reviewed in detail (14).

The PIVOT study (15) was a randomized, controlled, non-inferiority trial comparing PI monotherapy with standard of care (triple therapy) as maintenance therapy in HIV-1-infected adults with baseline HIV-1 VL <50 copies/mL ($n=587$). The choice of PI/r was at the discretion of the investigator, and the primary outcome was non-inferiority of the PI/r monotherapy group in terms of loss of future drug options, defined as new intermediate-level or high-level resistance to ≥ 1 antiretroviral drug, to which the patient's virus was susceptible at study entry. Viral rebound was more frequent in the PI/r monotherapy group (35% c.f. 3.2%, 95% confidence interval: 24.6–39, $p<0.0001$); however, reintroduction of NRTIs resulted in rapid virologic suppression (15).

In light of the above studies, boosted LPV and DRV may be considered as monotherapy in certain populations, with regular monitoring of VL and reintroduction of combination therapy in cases of viral rebound. The use of ATV/r as monotherapy cannot be recommended. Concerns persist about virologic escape in the CSF and the development of CNS disease in subjects receiving PI monotherapy, and this combination is not recommended in HBV coinfection. In addition, real-world studies report a higher incidence of virological failure and emergent resistance than has been described in clinical trials (16).

DUAL REGIMENS

Two drug regimens (2DR) allow class-sparing and may be safer and more tolerable than conventional therapy and more efficacious than monotherapy (17). Although early studies comparing 2DR to triple therapy reported higher rates of treatment failure, the availability of newer drugs with a higher barrier to resistance has led to a resurgence of interest in these regimens as both initial and continuation therapies for HIV infection.

Treatment naive

The use of PI-based dual ART has been explored in a number of combinations, and while not recommended as first-line treatment, these 2DRs are deemed acceptable for use when there is a need to avoid certain antiretroviral classes. Both the European (5) and American (4) guidelines allow the use of boosted DRV and RAL as an NRTI sparing combination provided baseline HIV-1 VL <100,000 copies/mL and CD4 >200 cells/mm³. In select circumstances, the use of a boosted PI and single NRTI may be considered (4); however, the data are not as extensive for this combination and it is not included in the British or European guidelines (3, 5). DTG plus 3TC may also be considered as an alternative combination where other NRTIs cannot be used (4, 5).

Various combinations of PIs and INSTIs have been explored as 2DRs in ART naive individuals. In the PROGRESS study (18), boosted LPV and RAL were compared to triple therapy with TDF/FTC and LPV/r. The 2DR combination was found to be non-inferior to the NRTI-containing regimen in terms of virological efficacy, and both regimens demonstrated comparable safety and

tolerability. At 96 weeks, 66.3% of subjects receiving RAL and LPV/r and 68.6% of those receiving triple therapy achieved virologic suppression. However, this study was limited by the low proportion of subjects with baseline HIV RNA >100,000 copies/mL. Similarly, the SPARTAN trial (19) showed that twice-daily administration of ATV and RAL in ART naive individuals achieved virologic response rates at week 24 comparable to triple therapy (HIV RNA <50 copies/mL 74.6% and 63.3%, respectively). Nevertheless, the combination was not considered optimal for further development due to higher rates of Grade 4 hyperbilirubinemia in the dual therapy group, and the emergence of INSTI-resistance associated mutations in subjects failing on the 2DR regimen (19). The combination of DRV and RAL has also been explored as initial therapy in HIV infection with mixed results. In the RADAR study, DRV/r plus RAL did not achieve comparable week 48 virologic efficacy to TDF/FTC and DRV/r (proportion achieving HIV RNA <50 cells/mL 60% and 83.7%, respectively, $p=0.045$), although no treatment-emergent resistance-associated mutations were identified in either group (20). In the NEAT 001/ANRS 143 study (21), DRV/r and RAL were found to be non-inferior to standard therapy with DRV/r and TDF/FTC at 96 weeks (21) although, in individuals with baseline CD4 <200 cells/mm³, the NRTI sparing regimen was less efficacious (proportion of failure at week 96 43.2% c.f. 20.9%). Both studies found that RAL-based regimens were associated with significantly less loss of bone mineral density in comparison to the TDF containing regimen.

INSTIs have also been studied in combination with 3TC: The PADDLE study ($n=20$) was a small pilot study exploring DTG and 3TC as first-line therapy in treatment-naive subjects (22). At week 48, 90% of subjects reached the primary end point of plasma VL <50 copies/mL. Of note, one patient committed suicide before study completion and the neuropsychiatric adverse events associated with DTG remain a concern. In the ACTG 5353 study ($n=120$), DTG/3TC was compared to conventional cART for treatment-naive subjects with baseline HIV-1 VL <500,000 copies/mL (23). DTG/3TC was found to be non-inferior to triple therapy, although one individual who developed virologic failure on the dual regimen subsequently developed NRTI and integrase resistance mutations (M184V and R263R/K) (23). Subsequent data from the GEMINI series ($n=1441$), two large, multi-center, randomized, non-inferiority, phase 3 trials also evidenced non-inferiority of DTG plus 3TC compared to triple therapy as initial therapy in HIV-1 adults with baseline VL <500,000 copies/mL (% VL <50 copies/mL at 48 weeks 90% and 93% respectively) and treatment-emergent INSTI resistance was not demonstrated (24).

DHHS guidelines allow the use of DRV/r plus 3TC for HIV-1-infected individuals who cannot take ABC, TAF, or TDF, on the basis of preliminary data from the unpublished ANDES study ($n=145$) (4). The fixed dose combination of DRV/r (800/100mg) and 3TC was found to be non-inferior to triple therapy, with 93% of subjects on the 2DR regimen and 94% of individuals receiving triple therapy achieving HIV-1 VL <50 copies/mL at 48 weeks. The combination of a boosted PI and NRTI was also explored within the GARDEL study: LPV/r plus 3TC ($n=426$) was non-inferior to triple therapy in terms of virologic outcome and was better tolerated (25). However, the need for twice-daily dosing and high pill burden of this combination limits its real-world applicability.

Data on the use of boosted PIs together with an NNRTI are less promising. The use of LPV/r and EFV (NRTI sparing group) was compared to LPV/r and two NRTIs (LPV/r group) and EFV and two NRTIs (EFV group), as initial therapy for HIV infection (26). The virologic efficacy of the NRTI sparing combination was found to be similar to that of the EFV group, and the groups did not differ in time to discontinuation due to side effects. However, NNRTI resistance mutations were more frequent in the NRTI-sparing group and the NRTI-sparing combination underperformed in HIV-infected subjects with HIV-1 RNA >100,000 copies/mL.

The CCR5-inhibitor maraviroc (MVC) has been used in combination with a number of PIs in the ART-naive setting for patients with R5 tropic virus. The A4001078 study compared ATV/r and MVC to ATV/r and TDF/FTC and found that overall rates of virologic suppression at 48 weeks were similar between groups (74.6% and 83.6%, respectively) (27). However, the study was underpowered to establish non-inferiority, and when stratified by HIV-1 RNA at baseline, the proportion of subjects achieving viral suppression was higher in the TDF/FTC arm (27). Pulido et al. (28) also investigated this combination and found that MVC and ATV/r was associated with comparable immunovirologic efficacy to a triple-drug regimen at 48 weeks. In addition, the combination of LPV/r and MVC was shown to be comparable to triple therapy in terms of virologic response, and to demonstrate greater immunological benefit (29). In contrast, the MODERN study, comparing DRV/r and MVC (150 mg od) to TDF/FTC/DRV/r, found that the 2DR combination was statistically inferior to the NRTI containing regimen, and the study was terminated early (30). Given these conflicting data, the combination of MVC and boosted PI cannot be recommended as first-line therapy in ART-naive individuals at present.

Treatment experienced

Dual regimens have been explored as switch options in the setting of virologic suppression to prevent or ameliorate drug toxicity, to avoid drug-drug interaction, and to reduce pill burden. Knowledge of previous drug resistance and an accurate antiretroviral drug history is essential if this switch is considered, and agents with activity against HBV must be continued in coinfecting subjects. At present, the European and American guidelines recommend the combination of a boosted PI (DRV/r or DRV/c, or ATV/r or ATV/c) together with 3TC (4, 5). Boosted LPV may also be used. The combination of the INSTI DTG plus the NNRTI RPV may be considered as an alternative (5).

The combination of a boosted PI/r and 3TC has been explored in several studies (17, 31–34). The MOBIDIP study (17) (n=265) was a randomized, multicenter superiority trial conducted in Sub-Saharan Africa, comparing maintenance therapy with a boosted PI (LPV/r or DRV/r) to dual therapy with 3TC plus either boosted PI. The 2DR was found to be superior to PI/r monotherapy in terms of virologic efficacy, and Grade 3 or 4 serious adverse events were less frequent (17). In the DUAL-GESIDA study (34) (n=249), DRV/r plus 3TC was shown to be non-inferior to DRV/r and 2NRTI in terms of virologic efficacy, with similar tolerability. Similarly, the OLE study (n=250) found that LPV/r plus 3TC was non-inferior to triple therapy as maintenance in virologically suppressed patients and demonstrated comparable safety (33). Boosted ATV has been studied in combination with 3TC in the SALT (31) (n=285) and ATLAS-M trials (32) (n=266) with equally

encouraging results. Both studies demonstrated that switching from triple therapy to ATV/r plus 3TC succeeding in maintaining virologic suppression, and the ATLAS-M study showed that switching from a TDF-containing regimen was associated with improved renal parameters (32).

Combinations of boosted PIs together with INSTIs have been investigated, with variable outcomes. Overall study sizes are small, and further research is required before these combinations are recommended.

Finally, the NNRTI RPV has also been used in a variety of 2DRs. The combination of RPV plus DTG was investigated in the SWORD series, two multi-center, randomized, non-inferiority studies conducted across 12 countries (35). Switching to DTG plus RPV was non-inferior to continued cART, with 95% of participants achieving VL <50 copies/mL at 48 weeks in both the groups; however, treatment discontinuation due to adverse event was more frequent in the 2DR group (35). RPV has also been used in combination with DRV/r in the PROBE study and with the novel INSTI cabotegravir (CAB) in the LATTE studies (36, 37). The PROBE study was a small (n=60) randomized controlled trial comparing DRV/r plus RPV to PI/r plus 2NRTI as maintenance in virologically suppressed patients. DRV/r plus RPV demonstrated non-inferior virologic efficacy, and patients on the 2DR showed improvement in markers of bone metabolism (38). The LATTE study was a dose-ranging, multi-center, randomized trial conducted in the US and Canada, exploring the use of dual therapy with oral CAB plus RPV after induction with CAB plus 2NRTIs (36). The control arm was EFV plus 2NRTIs. CAB plus RPV demonstrated similar antiviral activity and was well tolerated in comparison to the EFV-based regimen (36).

While an attractive option for HIV-1-infected subjects wishing to limit ART exposure, 2DRs cannot be recommended for all. Questions remain about the long-term efficacy of these combinations, and real-world data on their use in women, older adults, coinfecting patients, and people who inject drugs are limited. Furthermore, caution should be demonstrated when using these combinations as first-line therapy in individuals with baseline HIV-1 VL >100,000 copies/mL and CD4 cell count <200 cells/mm³. At present, data are lacking on the use of salvage therapy for individuals who fail a dual antiretroviral regimen, and concerns persist about the development of drug resistance in these subjects.

DIFFERENT ART FORMULATIONS

Another strategy to improve the tolerability of ARVs is through the use of new long-acting antiretroviral formulations to reduce dosing frequency.

Long-acting injectable formulations of both CAB and RPV are in development, and their use as maintenance therapy in virologically suppressed subjects was evaluated in the LATTE-2 (37) trial (n=286). Following a 20-week induction of oral CAB plus ABC/3TC, virologically suppressed individuals were randomized to intramuscular (IM) injections of RPV plus CAB at 4-weekly or 8-weekly intervals or continued oral cART. Both 4-weekly and 8-weekly administration of IM RPV plus CAB was found to be as effective at maintaining HIV-1 viral suppression through 96 weeks (37). Furthermore, despite a significant proportion of patients reporting side effects, predominantly injection site reactions, the majority of

study participants preferred the long-acting agent to the oral equivalent. Results from the phase 3 FLAIR (<https://clinicaltrials.gov/ct2/show/NCT02938520>) and ATLAS studies (<https://clinicaltrials.gov/ct2/show/NCT02951052>), evaluating the use of monthly long-acting injections of CAB/RPV as maintenance therapy, are awaited, and preliminary data are encouraging.

NOVEL ANTIRETROVIRAL AGENTS

Experimental strategies to reduce the HIV-1 viral reservoir through reversal of HIV latency, i.e., through histone deacetylase inhibition and targeting of immune checkpoint molecules, are intriguing but beyond the scope of this review. However, there remain a number of other investigational agents in the development pipeline. Data on the use of ibalizumab, a monoclonal antibody which binds non-competitively to CD4 cells to block HIV-1 attachment, are encouraging. Ibalizumab demonstrated significant antiviral activity in combination with a background antiretroviral regimen in subjects with advanced multidrug-resistant (MDR) HIV-1 infection (n=40), with limited treatment options (39). However, of the patients who developed virologic failure or rebound (n=10), 90% demonstrated diminished susceptibility to ibalizumab, which may limit its use in future.

Fostemsavir is a prodrug of the attachment inhibitor temsavir, which binds directly to HIV-1 gp120 to block initial viral attachment and entry into CD4 cells. Its use has been studied in highly treatment-experienced HIV-1-infected subjects, where it demonstrated similar virologic and immunologic responses to the control arm (40). The 48 week data from the BRIGHT study (41, 42), a phase 3 trial of the addition of fostemsavir to an optimized background regimen as salvage therapy in heavily treatment-experienced HIV-1-infected subjects with baseline HIV VL >400 copies/mL, were recently reported. The study consists of two arms: a randomized, placebo-controlled arm including individuals with ≤ 2 active ART classes remaining and an open-label arm consisting of individuals with no remaining fully active agents. Other investigational drugs, including ibalizumab, were allowed during the optimization stage. Promisingly, at week 48, 54% of participants in the randomized study (146/272) and 38% (38/99) in the open-label study had viral load <40 copies/mL.

CONCLUSION

Research continues apace to improve the safety, efficacy, and tolerability of ART for HIV-1 infection. While the use of PI monotherapy for the treatment of both ART-naive and treatment-experienced individuals remains controversial, data on the use of 2DRs in select cases are promising. At present, injectable ART formulations are associated with significant adverse effects yet were preferred by study participants and may prove an attractive option for subjects wishing to reduce their pill burden. Finally, preliminary results for the novel antiretroviral agents, fostemsavir and ibalizumab, are encouraging, and these drugs represent a ray of hope for MDR-HIV-infected individuals for whom few treatment options remain. Clinicians working in the field of HIV medicine must familiarize themselves with these novel antiretroviral strategies to provide optimized, individualized care for their patient body.

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