Review Article

Integrative Clinical and Practical Hematology

Highlights of Antiretroviral Therapy for Adults and Adolescents Patients with HIV Infection in the Technological Era

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Abstract

Significant advances in antiretroviral therapy have been made since the introduction of Zidovudine (AZT) in 1987 but in the “Technological Era” 36.7 million people are infected with HIV worldwide with a dramatic increase of adolescent and young (40%) of new HIV Infections. The news antiviral cocktails can reduce HIV in patients experienced, prolong survival, and prevent HIV transmission. In the Technological Era Combination Antiretroviral Therapy (cART) containing preferably three active drugs from two or more classes is required for sustained virologic suppression. Regimen selection is based on virologic efficacy, limited side effects, resistance test results, comorbid conditions, social status, and cost. With prolonged virologic suppression, improved clinical outcomes, and longer survival, patients will be exposed to antiretroviral agents for decades. Therefore, maximizing the safety and tolerability of cART is a high priority. Emergence of resistance and/or lack of tolerability in individual patients require availability of a range of treatment options. Development of new drugs is focused on improving safety (e.g. tenofovir alafenamide) and/or resistance profile (e.g. doravirine) within the existing drug classes, combination therapies with improved adherence (e.g. single-tablet regimens), novel mechanisms of action (e.g. attachment inhibitors, maturation inhibitors, broadly neutralizing antibodies), and treatment simplification with infrequent dosing (e.g. long-acting injectables). In parallel with cART innovations, research and development efforts focused on agents that target persistent HIV reservoirs may lead to prolonged drug-free remission and HIV cure.

Keywords: HIV-1 infection, Antiretroviral therapy

Introduction

The Human Immunodeficiency Virus (HIV) was discovered in 1982, but treatment strategies were not introduced until 5 years later [1]. The 2018 has been an important year for HIV research. There were five new approvals of new drugs or Fixed Dose Combinations (FDCs), including the first in class monoclonal antibody, but not all drugs have been approved yet in both the US and the EU, and one, was only approved in China.

Unfortunately in this “Technological ERA” the UNICEF (Report Children, HIV and AIDS, Johannesburg 29 November 2018) estimates that 360,000 adolescents are projected to die of AIDS-related diseases between 2018 and 2030. This means 76 adolescent deaths every day – without additional investment in HIV prevention, testing and treatment programmers.
Adolescents (represent over 40% of new HIV infections globally) are sometimes characterized by high-risk sexual behavior and a lack of engagement with healthcare services that can affect adherence to Antiretroviral Therapy (ART). Despite adherence to ART being critical in controlling viral replication, maintaining health and reducing onward viral transmission, there are limited data on ART adherence.

The paradigm established in the late 1990s is the cART Combination antiretroviral therapy, responsible for the dramatic decline in AIDS deaths and is composed of two Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) plus a third active drug from a different class. Contemporary HIV treatment is highly effective at suppressing plasma viremia, and significant progress has been made toward regimen simplification through the combination of three active drugs into Single-Tablet Regimens (STRs) and optimization of drug profiles that maximize long-term tolerability and safety. Lifelong, chronic therapy without treatment interruption is the standard of care, and the availability of multiple effective drugs in several classes with differing resistance, safety, and tolerability profiles provides choices after failure of first-line treatment [1,2].

Goals of HIV combination therapy

Eradication of HIV cannot be achieved with current cART due to the pool of latently infected CD4 T cells established early during acute infection. However, cART can reduce HIV-associated morbidity, prolong survival, and prevent HIV transmission [1-5]. Maximal and durable suppression of plasma viremia restores and preserves immunologic function, delays or prevents the development of drug-resistant mutations, and may also decrease the immune activation and inflammation thought to contribute to end-organ damage [6-8]. Suppressing plasma viremia below detection limits is possible within weeks of therapy and depends on adherence to an efficacious regimen.

Morbidity and mortality in HIV-infected subjects is increasingly driven by non-AIDS associated comorbidities such as kidney, liver, and heart disease [9,10] (Linley L et al., Abstract B08-1, 2007 National HIV Prevention Conference, Atlanta, GA, December 2007). Even with cART, aging patient populations with HIV-1 infection experience more age-related comorbidities, such as diabetes, and cardiovascular, renal, and bone disease, which manifest earlier than in HIV-uninfected peers [11]. With prolonged virologic suppression, improved clinical outcomes, and longer survival, patients may be exposed to antiretroviral agents for decades [12]. Thus, maximizing the safety and tolerability of cART regimens while maintaining strong clinical efficacy is a high priority.

Regimens for first-line therapy and Guidelines

Therapy used to be initiated based on decreasing CD4 cell count or clinical evidence of AIDS. More recently, therapy is being initiated regardless of the CD4 cell count, often immediately after a patient’s diagnosis, a clinical decision in part facilitated by the improved tolerability and safety of contemporary cART drugs. Antiretroviral regimens that contain at least two and preferably three active drugs from two or more classes are recommended for virologic suppression (Table 1). Initial therapy generally consists of two NRTIs combined with a third agent such as an Integrase Strand Transfer Inhibitor (INSTI), a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), or a pharmacologically boosted Protease Inhibitor (PI). Global and regional guidelines have generally consistent recommendations for first-line therapy (Table 2); US and European guidelines have begun to emphasize INSTIs because of their high virologic efficacy and excellent safety and tolerability profiles (e.g. Federally approved HIV/AIDS medical practice guidelines; URL: https://aidsinfo.nih.gov/guidelines). Efavirenz and atazanavir are no longer recommended because of long-recognized tolerability and safety concerns and the availability of better alternatives. Boosted PI-based treatment maintains clinical value due to high genetic barrier to resistance in patients at high risk for intermittent therapy because of poor adherence.

Recommended NRTIs are Tenofovir Disoproxil Fumarate (TDF) or Abacavir (ABC) used in combination with emtricitabine (FTC) or lamivudine (3TC). Although potent and generally well tolerated, TDF may cause clinically significant renal toxicity and is associated with greater reductions in bone mineral density than other antiretrovirals [13-16]. The novel prodrug Tenofovir Alafenamide (TAF) delivers approximately four-fold higher intracellular levels of the active metabolite tenofovir diphosphate at one-tenth of a dose relative to TDF, allowing for much lower doses of TAF versus TDF [17]. This lowers the plasma exposure of tenofovir by 90% relative to TDF, thereby reducing the risk of tenofovir-associated off-target effects. Another commonly used NRTI, ABC, is a preferred NRTI when co-administered with 3TC and Dolutegravir (DTG). ABC is also associated with drug hypersensitivity, requires testing for the HLA B*5701 allele, and may be linked to increased rates of myocardial infarction [18-20]. Generally, selection of a regimen is
<table>
<thead>
<tr>
<th><strong>Compound/Company Approved</strong></th>
<th><strong>Class</strong></th>
<th><strong>Comment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>darunavir/cobicistat/TAF/FTC</td>
<td>Boosted PI and NRTI FDC</td>
<td>The first single-pill protease inhibitor-based FDC. It needs to be taken with food. Trade name: Symtuza.</td>
</tr>
<tr>
<td>Janssen and Gilead</td>
<td></td>
<td></td>
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<tr>
<td>bicitravir/FTC/TAF</td>
<td>INSTI and NRTI FDC</td>
<td>Once-daily, unboosted, low mg FDC with FTC/TAF that can be taken with or without food. Trade name: Biktarvy.</td>
</tr>
<tr>
<td>Gilead</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dolutegavir/ rilpivirine FDC</td>
<td>INSTI and NNRTI FDC</td>
<td>New two-drug coformulation approved as maintenance therapy in patients with undetectable viral load. Trade name: Juluca.</td>
</tr>
<tr>
<td>Viiv and Janssen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>mAb</td>
<td>Intravenous infusion given every two weeks and approved for people with multiclass HIV drug resistance. Trade name: Trogarzo.</td>
</tr>
<tr>
<td>TaiMed and Theratechnologies</td>
<td>CD4 binding</td>
<td></td>
</tr>
<tr>
<td>Albuvirtide</td>
<td>Entry inhibitor</td>
<td>Once-weekly infusion (Similar to T-20) but improved PK and safety profile. Currently only available in China. Trade name: Aikening.</td>
</tr>
<tr>
<td>Frontier Biotech</td>
<td></td>
<td></td>
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<tr>
<td>Submitted applications or completed phase 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>doravirine</td>
<td>NNRTI</td>
<td>Active against first generation NNRTI resistance. Non-inferior to efavirenz. Regulatory decision expected 3Q2018.</td>
</tr>
<tr>
<td>Merck/MSD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>doravirine/TDF/FTC</td>
<td>NNRTI and NRTI FDC</td>
<td>FDC using doravirine with two generic NRTIs. Regulatory decision expected 3Q2018.</td>
</tr>
<tr>
<td>Merck/MSD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dolutegravir/3TC</td>
<td>INSTI and NRTI FDC</td>
<td>Phase 3 GEMINI studies as initial ART are complete, switch study TANGO is ongoing. Regulatory decision expected 3Q2019.</td>
</tr>
<tr>
<td>Viiv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fostemsavir (GSK3684934)</td>
<td>ap120 attachment inhibitor</td>
<td>Phase 3 BRIGHTE study completed with 24-week results in treatment-experienced with extensive drug resistance. Regulatory application not yet submitted.</td>
</tr>
<tr>
<td>Viiv</td>
<td></td>
<td></td>
</tr>
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Table 2: Recommended antiretroviral regimens for treatment-naïve patients based on US DHHS guidelinesa.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Components</th>
<th>STR available</th>
<th>Comment</th>
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</thead>
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<tr>
<td>NRTI</td>
<td>NRTI</td>
<td>Third agent</td>
<td></td>
</tr>
<tr>
<td>INSTI-based</td>
<td>ABC</td>
<td>3TC</td>
<td>DTG</td>
</tr>
<tr>
<td>TDF</td>
<td>FTC</td>
<td>DTG</td>
<td>No</td>
</tr>
<tr>
<td>TDF</td>
<td>FTC</td>
<td>EVG/COBI</td>
<td>Yes (Stribild) Only for patients with pre-antiretroviral therapy CrCl &gt;70 mL/min</td>
</tr>
<tr>
<td>TAF</td>
<td>FTC</td>
<td>EVG/COBI</td>
<td>Yes (Genvoy) Only for patients with pre-antiretroviral therapy CrCl ≥30 mL/min</td>
</tr>
<tr>
<td>TDF</td>
<td>FTC</td>
<td>RAL</td>
<td>No</td>
</tr>
<tr>
<td>PI-based</td>
<td>TDF</td>
<td>FTC</td>
<td>DRV/RTV No</td>
</tr>
</tbody>
</table>

3TC: lamivudine; ABC: abacavir; COBI: cobicistat; CrCl: creatinine clearance; DHHS: Department of Health and Human Services; DRV: darunavir; DTG: dolutegravir; EVG: elvitegravir; FTC: emtricitabine; INSTI: integrase strand transfer inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; RAL: raltegravir; RTV: ritonavir; STR: single-tablet regimen; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

centered on individual patients’ needs based on virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions, and cost.

Based on guidelines developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents (https://aidsinfo.nih.gov/guidelines).

Prevention as the “First treatment” in the” Globally technological Era”

Despite advances in the prevention and treatment of HIV infection, the rate of new infections has remained relatively unchanged over the past decade [21]. Now substantial efforts to prevent the new HIV infection in adolescent and young (dramatic increase in the “Technological Era”) have focused on:

1. Improved access to and demand for HIV testing and counselling, treatment and care.
2. Improved management of care and the transition of adolescents from pediatric to adult care particularly addressing adherence, disclosure and retention.
3. Development and empowerment of adolescents and youth through improved access to quality health care, protection, education and skills development including gender-sensitive comprehensive sexuality education.

In HIV-infected individuals, low plasma HIV RNA is associated with decreased concentration of virus in genital secretions [22-24], and HIV transmission risk is low when plasma viral loads are <400 copies/mL [25]. In communities with high concentrations of HIV-infected individuals, the use of cART is associated with decreased community viral load and reduced rates of new HIV diagnoses [26-28]. Recent clinical evidence
strongly supports the value of antiretroviral treatment as prevention in sero-discordant couples; patients taking cART had a 96% reduction in HIV transmission to their uninfected partners [29].

**Management of treatment-experienced patients**

While current antiretroviral regimens for treatment-naïve patients are highly effective and well tolerated, a regimen change may be needed in individual patients because of a lack of virologic suppression, drug adverse effects, or avoidance of drug–drug interaction with other medications [30]. Therapeutic goals for experienced patients remain the same as for naive patients: maintaining suppression of virus replication while enabling immune recovery and minimizing adverse drug effects. This requires a highly individualized approach and frequent monitoring as well as navigating the challenges of more limited treatment options.

Treatment guidelines are important sources of information for the management of treatment-experienced subjects and include recommendations for drug resistance testing, management of drug-related adverse effects, and drug–drug interactions (Federally approved HIV/AIDS medical practice guidelines; URL: https://aidsinfo.nih.gov/guidelines).

If a regimen change is needed due to resistance, ideally the new regimen should contain at least two or, preferably, three fully active drugs [30]. New regimen construction requires careful review of patient treatment history and resistance testing. Genotypic resistance testing is routinely used as it is faster and cheaper than phenotypic testing and can quickly detect resistance due to the presence of known well-characterized mutations in the target viral gene(s).

Virologic failure on the currently recommended first-line cART regimens due to emergence of drug resistance is rare [31-33]. Resistance emergence could be more frequent in NNRTI-containing first-line regimens compared with those containing boosted PIs [34] or INSTI [35]. Patients with multi-class resistance are undoubtedly the most challenging group to treat because of limited options. Depending on the nature and extent of the resistance, the options may include drug classes not generally recommended for initial therapy, such as entry inhibitors maraviroc (CCR5 inhibitor) or enfuvirtide (gp41 fusion inhibitor). Additional antiretroviral classes such as Gag maturation inhibitors and gp120 entry inhibitors are in clinical testing and could become valuable options for individuals with multi-class resistance.

Another reason for changing an existing regimen can be adverse effects and lack of tolerability. Examples include Central Nervous System (CNS) toxicity associated with NNRTIs, particularly efavirenz, and lipid changes or gastrointestinal toxicity associated with boosted PIs [35]. After elimination of thymidine analogs from first-line therapy and introduction of pre-screening for ABC hypersensitivity, NRTI-associated toxicity is relatively rare and includes ABC-associated cardiovascular and lipid effects, and TDF-associated renal and bone effects. TAF, the novel prodrug of tenofovir, significantly reduces the renal and bone effects associated with TDF [36], and multiple switch studies from TDF to TAF are in progress (ClinicalTrials.gov Identifiers: NCT02345252 and NCT02345226). An alternative strategy could be a switch to an NRTI-sparing regimen. For example, an NRTI-sparing once-daily DTG + Rilpivirine (RPV) regimen is being tested in Phase 3 switch studies [37] (NCT02429791 and NCT02422797).

**New drugs in clinical development**

Several new drugs from clinically validated classes are in advanced stages of development. Doravirine (formerly MK-1439) is a potent novel NNRTI with a favorable resistance profile as it remains active against viruses with K103N and Y181C mutations [38,39]. Doravirine reduced HIV viral load by about 1.3 log in a 7-day monotherapy study [38]. Similar efficacy to efavirenz was shown in a follow-up study, but with fewer side effects, especially CNS-related, following treatment in combination with TDF/FTC [40]. Cabotegravir (formerly GSK1265744) is an orally bioavailable INSTI chemically related to DTG with potent activity and a long half-life [41,42]. Oral cabotegravir has shown antiretroviral efficacy in a short-term monotherapy trial [41], and an injectable nanosuspension-based formulation administered subcutaneously or intramuscularly once every 4–8 weeks resulted in sufficient systemic drug exposures [43] and was effective as a long-acting therapy in combination with RPV (Margolis D et al., Abstract 31LB, CROI, Boston, MA, February 2016). GS-9883 is another novel unboosted INSTI currently being tested in treatment-naive HIV-infected patients in combination with TAF and FTC (NCT02607930 and NCT02607956).

Among the antiretrovirals with novel mechanisms, BMS-663068 (fostemsavir) is an oral prodrug of HIV attachment inhibitor BMS-626529 [44]. BMS-626529 inhibits HIV entry into CD4 cells by binding to the
gp120 envelope protein and preventing a conformational change that is normally required to bind HIV co-receptor [45]. In a Phase 2b, randomized, active-controlled trial in treatment-experienced subjects virologic response rates and immunologic reconstitution were similar across the BMS-663068 and ritonavir-boosted Atazanavir (ATV/r) arms through week 48 (Thompson M et al., Abstract 545, CROI, Seattle, WA, February 2015).

Maturation inhibitors represent another novel class of antiretrovirals that specifically interfere with processing of the p24/p1 cleavage site in Gag polyprotein, a distinct mechanism of virus maturation inhibition from that exerted by HIV PIs. BMS-955176 is an oral once-daily second-generation maturation inhibitor with improved potency against HIV variants with Gag polymorphism over the first-generation inhibitors (Protack Y et al., Abstract, 15th European AIDS Conference, Barcelona, Spain, October 2015). In a proof-of-concept monotherapy study, 10-day dosing of BMS-955176 resulted in plasma viral load reduction of up to 1.7 log_{10} copies/mL (Hwang C et al., Abstract 114LB, CROI, Seattle, WA, February 2015). In combination with ATV +/- Ritonavir (RTV), BMS-955176 was well tolerated and showed clinical efficacy (Hwang C et al., Abstract PS10/5, 15th European AIDS Conference, Barcelona, Spain, and October 2015). GSK2838232 is another second-generation maturation inhibitor active against HIV isolates resistant to bevirimat (Jeffrey J et al., Abstract 538, CROI, Seattle, WA, and February 2015). Its clinical development began by testing it alone and in combination with RTV in healthy subjects (NCT02289495).

Broadly Neutralizing Antibodies (bNabs) targeting the viral envelope have been tested in small proof-of-concept Phase 1 monotherapy studies. Antibodies 3BNC117 and VRC01 have shown HIV suppression in several subjects, but resistance emergence and/or preexisting HIV variants refractory to the treatment are among current concerns [46,47]. In contrast to bNabs, the antibody PRO140 targets CXCR5 co-receptor and provided sustained virologic suppression in a Phase 2b study in HIV-infected subjects who switched from their suppressive antiretroviral therapy to a subcutaneously self-administered monotherapy with PRO140 once weekly for >1 year (Cytodyn press release; URL: http://www.cytodyn.com/media/press-releases/detail/223/cytodyn-reports-full-virologic-suppression-in-eleven-hiv).

Future directions of HIV treatment for adults and adolescent

In addition to durable efficacy, safety and tolerability will continue to play an important role in the long-term success of HIV therapies. Further simplification of antiretroviral regimens will likely be a focus of future clinical development [48].

An emergency exists in this Technological Era: an estimated 1.9 million children and adolescents will still be living with HIV in 2030, mostly in Eastern and Southern Africa (1.1 million), followed by West and Central Africa (571,000), and Latin America and the Caribbean (84,000). The Report UNICEF (Children, HIV and AIDS, Johannesburg 29 November, 2018) points to two major “shortfalls” in the HIV response for children, adolescents and young adults: Slow progress in preventing HIV among young, and a failure to address the structural and behavioural drivers of the epidemic. Many adolescents do not know whether they have HIV or not, and among those who have been found HIV-positive and put on treatment, very few adhere to that treatment.

To address these persistent gaps, the last Report recommends a number of approaches, supported by UNICEF, including: family-centered testing to help identify and treat children living with HIV but not yet diagnosed; more diagnostic technologies at the point of care to improve early infant diagnosis; greater use of digital platforms to improve HIV knowledge among adolescents; adolescent-friendly services; and targeted community outreach for adolescents.

We can’t win the fight against HIV if we don’t accelerate progress in preventing transmission to the next generation. We must maintain the sense of urgency to sustain gains made in the past decade – for both boys and girls. And to do this we must look to innovative and preventative ways of reaching the most vulnerable and at-risk young people.

These advancements in the development of new antiretroviral therapies and treatment paradigms will be happening in parallel with the increased availability of generic antiretrovirals. In the absence of an efficacious vaccine, the effective and widespread use of antiretrovirals for treatment and prevention is the key approach to curb the global AIDS epidemics. Therefore, these innovations will be essential to achieve the ambitious goals in global implementation of antiretroviral therapy. In 2014, UNAIDS set a ‘90–90–90’ target aiming to diagnose 90% of all people infected with HIV, provide treatment for 90% of those diagnosed, and achieve full viral suppression in 90% of those on treatment by 2020 (UNAIDS; URL: http://www.
This translates into successfully treating >70% of all individuals infected with HIV, representing almost 25 million people worldwide.

In parallel with antiretroviral therapy innovations, research and development efforts are expanding toward new therapeutic approaches for targeting persistent HIV reservoirs that may lead to prolonged drug-free remission of the infection and potentially to HIV cure [49,50].

These new directions are focused on latency-reversing agents to activate the viral reservoirs, immunotherapies including innate immunity activators and effector antibodies, gene therapies, and therapeutic vaccines to eliminate the persistent viral reservoirs or induce effective immune control of HIV infection [51]. All these efforts are in early stages of testing, and long-term systematic research and commitment will be necessary to assess their true therapeutic potential. Ultimately, these technologies may lead to fundamental changes in the HIV healthcare [52].

Conflicts of interest

The authors do not have a commercial or other association that might pose a conflict of interest.

Reference


