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Beyond one pill, once daily: current challenges of antiretroviral therapy management in the United States

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Abstract

Introduction: Modern antiretroviral therapy (ART) has revolutionized HIV treatment. ART regimens are now highly efficacious, well-tolerated, safe, often with one multi-drug pill, once-daily regimens available. However, clinical challenges persist in managing ART in persons with HIV (PWH), such as drug-drug interactions, side effects, pregnancy, co-morbidities and adherence.

Areas Covered: In this review, we discuss the ongoing challenges of ART for adults in the United States. We review the difficulties of initiating ART and maintaining therapy throughout adulthood and discuss new agents and strategies under investigation to address these issues. A PubMed search was utilized to identify relevant publications and guidelines through July 2019.

Expert Opinion: Challenges persist in initiation and maintenance of ART. An individual's coexisting medical, social and personal factors must be considered in selecting and continuing ART to ensure safety, tolerability, and efficacy throughout adulthood. Continued development of new therapeutics and novel approaches to ART, such as long acting drugs or dual therapy, are needed to respond many of these challenges. In addition, future research must address therapeutic disparities for populations historically underrepresented in clinical trials, including women, people aging with HIV, and those with complex comorbidities.

Keywords

HIV; Antiretroviral therapy; women; aging; drug-drug interactions; non-AIDS-related comorbidities; Adults; AIDS

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Declaration of Interest

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1. Introduction

The advent of suppressive combination antiretroviral therapy (ART) has transformed HIV into a controllable, chronic disease. With modern ART, life expectancy for persons with HIV (PWH) now nears that of the general population[1]. Despite these advances, current optimal management of HIV requires that PWH remain on lifetime ART. Initiation and maintenance of ART throughout adulthood provide unique challenges for PWH and their care teams. In this paper, we provide an overview of the major challenges of ART management for adults with HIV in the United States. Our review and recommendations are based on the most recent United States ART guidelines and a PubMed search of articles available through July 2019.

2. History of Antiretroviral Therapy

Since the AIDS epidemic was first recognized in the United States in the early 1980s[2, 3], advances in ART have revolutionized care for PWH. Four decades of research have led to development of various antiretroviral medications that target key points in the HIV life cycle (Figure 1)[4]. Nucleoside analogues, which serve to terminate DNA synthesis, were the first class of medications to demonstrate activity against HIV [5]. Azidothymidine (AZT), originally created as a cancer drug, displayed potent activity against HIV but when used alone was associated with rapid development of viral resistance[6]. Additional nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) were developed, but viral resistance continued to limit their duration of activity. Over the next decade, new classes of medications including protease inhibitors (PIs), first approved in 1995, and non-nucleoside reverse transcriptase inhibitors (NNRTIs), first approved in 1996, became available[7]. By 1996, triple-drug combination, highly active antiretroviral therapy (HAART) comprised of 2 NRTIs plus either a PI or NNRTI became the new treatment standard with a subsequent marked decline in HIV-associated mortality rates [8, 9].

Additional medication classes including fusion/entry inhibitors, integrase strand transfer inhibitors (INSTIs), and post-attachment inhibitors continue to strengthen the HIV treatment armamentarium. The development of INSTIs, which are well-tolerated and have a high barrier to resistance, inaugurated another revolution in ART management. INSTI-containing three-drug regimens are now recommended for initial ART by US guidelines[10, 11].

3. Goals of ART

The goals of antiretroviral therapy are to achieve and maintain viral suppression to preserve immunity, reduce transmission, and prevent AIDS related morbidity and mortality. Early treatment of HIV has been associated with a higher likelihood of restoring CD4 counts and long-term preservation of T lymphocytes[12, 13]. The mortality benefits of early ART in HIV are now well established as detailed in sections below.

Treatment of PWH also serves an important public health role by reducing the risk of sexual, perinatal, and parenteral transmission of HIV. The landmark Pediatric AIDS Clinical Trials Group (PACTG) study 076 established that treating mothers with HIV and their newborn infants with ART dramatically reduced perinatal transmission of HIV[14]. Several large

trials have concluded that effective ART prevents sexual transmission of HIV. In the HPTN 052 randomized controlled trial among HIV serostatus-discordant, mostly heterosexual couples, the partners with HIV were randomized to early versus delayed start of ART[15]. The trial demonstrated a 93% reduction of HIV transmission among couples in the early ART group. There were 8 transmissions in the early start group, and all occurred when the partner with HIV had a positive viral load (prior to suppression or during virologic failure). No transmissions were detected when viral loads were completely suppressed. The PARTNER study evaluated gay serostatus-discordant male couples over an average of 2 years with greater than 76,000 condomless sexual encounters reported. During this study there were no phylogenetically linked within-couple transmissions[16].

4. When to Start ART

Current guidelines recommend initiation of ART in almost all PWH as soon as possible after diagnosis regardless of CD4 count[10, 11]. Historically, concern for development of drug resistance and the toxicities of early regiments often delayed ART initiation for PWH with a normal CD4 count. Development of safer, more efficacious ART has shifted this risk to benefit ratio in favor of treatment. Initiation of ART reduces morbidity and mortality and prevents progression to AIDS in PWH[17]. Two major trials have since demonstrated benefits of ART therapy irrespective of CD4 count[18, 19]. In the START trial, treatment-naïve PWH initiated on therapy with a CD4 count > 500 cells/microL had a decrease in serious AIDS and serious non-AIDs related events at interim analysis compared to those with a delayed therapy (<350 cells/microL). These dramatic findings resulted in early termination of the study[18]. Similarly, the TEMPRANO study randomized patients to either early verses delayed initiation of ART. Persons in the early start group demonstrated a decreased risk of death and severe HIV-related illnesses[11].

Immediate ART or rapid start--defined as initiation of antiretrovirals on the same day or up to 14 days after diagnosis--has shown success in multiple cohort and randomized controlled studies[20, 21, 22, 23, 24, 25, 26]. Immediate start protocols have been associated with significant improvement in retention of care, time to viral suppression, and viral suppression up to a year after initiation[20, 21, 22, 24, 25, 26, 27]. Among persons with acute HIV, rapid start has additional theoretical benefits of decreasing the symptoms of acute HIV, reducing transmission in setting of high-level viremia, and preventing seeding of viral reservoirs[15, 28, 29, 30, 31, 32, 33]. However, rapid start does require coordination between testing and treatment centers and resources to ensure immediate access to medications and timely follow-up care with an HIV specialist. While many care settings in the U.S. do not have adequate infrastructure to support immediate ART, current guidelines recommend initiating ART as soon as possible after diagnosis as long as the PWH is ready to commit to treatment[11].

Despite the shift toward earlier ART initiation for all PWH, certain opportunistic infections (OIs) must still delay HIV therapy. Persons with most OIs should be started on antiretroviral therapy within 2 weeks of diagnosis and initiation of appropriate treatment for the OI with close monitoring for the immune reconstitution inflammatory syndrome (IRIS) [10, 11, 34]. Exceptions include certain persons with tuberculosis (TB) and those with cryptococcal

meningitis due to potential complications from IRIS seen shortly after initiating ART. Individuals with TB and CD4 <50 cells/mm^3 should be started on ART within 2 weeks[35] and those with TB and CD4 ≥50 cells/mm^3 should be started on ART within 2–8 weeks[36]. ART should not be delayed until TB therapy is completed as this was associated with higher mortality[37]. PWH with tuberculous meningitis randomized to immediate ART did not have improved mortality and were noted to have more adverse events compared to delayed ART. Therefore, caution with early ART is recommended in this population[38]. For persons with HIV and cryptococcal meningitis, the optimal timing for ART initiation is unknown, but early ART (started within 1-2 weeks of diagnosis) has been associated with increased mortality compared to deferred therapy (after 5 weeks)[39]. ART in cryptococcal meningitis should be delayed at least 2 weeks until induction therapy is completed and possibly until completion of entire consolidation phase[10].

5. Choosing an Initial ART Regimen

HIV providers and PWH must consider many factors when selecting an ART regimen. For most PWH who are treatment naïve, guidelines recommend the initiation of an INSTI and 2 NRTIs[10, 11]. The newer, second-generation INSTIs, dolutegravir (DTG) and bictegravir (BIC), are generally preferred due to their high barrier to resistance, favorable side effect profile, and lack of a need for a pharmacologic booster. Recommended NRTIs are tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), emtricitabine (FTC), abacavir (ABC), or lamivudine (3TC). Alternative regimens include a 2 NRTIs plus either a boosted PI or an NNRTI. Certain scenarios may warrant use or avoidance of specific antiretrovirals. Important considerations for selecting an ART regimen include characteristics of the HIV infection itself, co-infections, co-morbidities and drug interactions, reproductive plans in women of child-bearing potential, access, and convenience (e.g., food requirements, pill burden).

5.1 HIV Characteristics

Potential antiretroviral resistance and HIV viral load must be considered prior to ART initiation. Baseline genotypic resistance testing to assess for transmitted drug resistance (TDR) is recommended for all PWH prior to starting ART. Rates of baseline resistance among treatment naïve individuals are variable based on region and risk factors for HIV acquisition. ART prescribing patterns can contribute to regional differences in TDR[40]. A recent observational cohort study assessed baseline resistance in over 4,000 treatment naïve individuals spanning 14 years and found that the overall rate of TDR was increasing, but the drug resistance mutations recovered did not affect the efficacy of current first line regimens[41]. Use of TDF/FTC as pre-exposure prophylaxis (PrEP) initially raised concerns that it may generate resistant HIV infections. However, transmitted drug-resistance mutations are rare in PrEP and have been primarily noted in individuals who were started on TDF/FTC when they in fact had acute HIV infection but had negative findings on screening antibody tests[42].

When starting ART prior to the availability of genotype results or HIV viral load, boosted PI- or INSTI-based regimens are favored for their high barrier to resistance and rapid

efficacy. For immediate start, favored regimens include DTG+(TDF or TAF)/FTC, BIC/TAF/FTC, or darunavir (DRV) boosted with ritonavir (r) or cobicistat (c) +TAF/FTC or TDF/FTC or TDF/3TC due to their higher barriers against resistance[11]. Prior to use of ABC, PWH must have a negative test for HLA B*5701 which evaluates for predisposition to development of abacavir hypersensitivity syndrome, a potentially life-threatening condition which can occur during the first few weeks of initiation. As a result, INSTI-based single tablet regimen DTG/ABC/3TC is not appropriate for use as a rapid start ART choice.

Pretreatment HIV RNA level and CD4 count also must be factored into ART selection. Certain regimens have shown higher rates of virologic failure—i.e. failure of the ART regimen to suppress the viral load below 200 copies/mL—in the setting of high HIV RNA levels or low CD4 levels pretreatment. As a result, rilpivirine (RPV)-based regimens, DRV/r + raltegravir (RAL), and ABC/3TC with efavirenz (EFV) or ritonavir-boosted atazanavir (ATV) are not recommended for individuals with a pretreatment HIV RNA level >100,000 copies/mL. Similarly, RPV-based regimens and DRV/r + RAL are not recommended for PWH with a pretreatment CD4 count less than 200 copies/mL[10].

5.2 Co-infections

Treatment for co-infections has a significant impact on ART selection. Globally, 5-20% of PWH are also co-infected with hepatitis B virus (HBV)[43]. Persons with HIV-HBV coinfections experience higher morbidity and mortality than those with HIV infection alone[43]. Lamivudine, emtricitabine, and tenofovir (both TDF and TAF) are active against both HBV and HIV. In individuals with HIV-HBV co-infection, 2 drugs in the ART regimen must be HBV-active to treat adequately HBV[10].

Up to 30% of PWH in the US also are co-infected with HCV[44]. Individuals with dual HIV-HCV infection are at increased risk of progressive liver disease, particularly if they have low CD4 T cell lymphocyte counts. While use of direct acting antivirals (DAAs) for the treatment of HCV has been equally efficacious in achieving sustained virologic response in HIV/HCV coinfected populations[45], providers must be cognizant of some drug-drug interactions between DAAs and ART. Use of PIs and pharmacoenhancers are contraindicated with many DAAs, but other ART classes can be co-administered[10, 46].

Treatment of active tuberculosis (TB), latent TB and nontuberculous mycobacterium (NTM) infections in PWH may have a substantial impact on ART selection. Rifamycins are the backbone of TB therapy and potent inducers of the CYP450, P-glycoprotein and uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes which cause increased metabolism of antiretrovirals. The current US Department of Health and Human Services (DHHS) Guidelines do not recommend use of rifampin and rifapentine with PIs, both boosted and unboosted, because of the potential for reduced levels of antiretroviral activity[10]. On the other hand, rifabutin, which is a substrate of the CYP450 enzyme system, may be used with PIs but requires dose-reduction (rifabutin 150 mg daily). Among the NNRTIs, only efavirenz (EFV) is recommended for use with rifamycins. With regards to INSTIs, BIC and cobicistat-boosted elvitegravir (EVG) are contraindicated with rifamycins. However, RAL can be administered with rifamycins[47]. Raltegravir should be increased to 800 mg twice daily if used with rifampin but can be given at 400 mg twice daily when used

with a rifabutin-containing TB regimen[10]. Dolutegravir can also be used but current data suggest that increasing the dose to 50 mg twice a day is recommended when used with rifampin but no dose increased was needed with rifabutin even at 300 mg daily[1, 10, 48, 49]. Within the NRTIs, TDF, ABC, 3TC, and FTC can be given together with rifampin-containing TB treatment without dose adjustment. TAF should be used with caution since PK and virologic efficacy with ART and TB regimens have not yet been completed[10].

5.3 Co-morbidities

The presence of chronic, non-infectious conditions also impact ART selection. While the safety and tolerability of modern ART has substantially improved compared to historical regimens, significant toxicities persist. In particular, ART effects on renal function, bone density, neuropsychiatric symptoms, and cardiometabolic risk have been seen[10].

HIV is an independent risk factor for renal disease[50]. ART can both decrease the risk of renal disease by treating HIV and contribute to nephrotoxicity[51, 52]. Tenofovir disoproxil fumarate (TDF) has been associated with nephrotoxicity, including proximal renal tubulopathy (Fanconi's Syndrome)[53]. These adverse effects of TDF are attributed to high circulating plasma levels of tenofovir. The newly formulated tenofovir alafenamide (TAF) is a tenofovir prodrug, which has increased intracellular delivery of the active moiety and lowers plasma circulating levels of tenofovir by 90%[54]. As a result, TAF has an improved safety profile and has demonstrated improved laboratory measures of renal function than TDF in a large non-inferiority study[55]. In PWH who have a pretreatment estimated glomerular filtration rate (eGFR) < 60 mL/min, TDF should be avoided. TAF can be used with an expanded eGFR >30 mL/min[10].

Compared to seronegative individuals, PWH have higher rates of osteopenia, osteoporosis and increased risk of fragility fractures[56]. In addition to its nephrotoxicity, TDF can cause decreased bone mineral density leading to osteopenia and osteoporosis[57]. As a result, TDF-containing regimens should be avoided in PWH starting ART who have known osteoporosis[10]. However, TAF has a favorable bone mineral density safety profile and can be used for these individuals[55].

PWH also suffer from increased rates of psychiatric illness and are at heightened risk for neurocognitive impairment (NCI)[58, 59]. Efavirenz and, to some extent, rilpivirine have been associated with neuropsychiatric symptoms and suicidality[60]. Therefore, EFV- and RPV- containing regimens are often avoided for PWH with known psychiatric illness. Recent data from cohort studies has indicated increased rates of neuropsychiatric adverse events with DTG[61, 62, 63]. Ongoing prospective studies are examining the mechanisms and clinical significance of this effect.

In addition, PWH experience higher rates cardiovascular disease than the general population[64, 65, 66]. This excess risk has been attributed to HIV-associated chronic inflammation and immune activation, ART-associated dyslipidemia and other cardiometabolic comorbidities, healthcare disparities, and increased tobacco use among PWH[64]. Dyslipidemia independently contributes to risk of atherosclerotic cardiovascular disease (ASCVD) in PWH[67]. Boosted-PIs, cobicistat and EFV are known to cause

dyslipidemia and may need to be avoided in individuals with known hyperlipidemia. In contrast, INSTIs are considered lipid neutral and TDF has a favorable lipid profile[10]. Furthermore, PWH experience high rates of metabolic comorbidities including diabetes[68], non-alcoholic fatty liver disease (NAFLD)[69], and body composition changes that can confer increased risk of cardiovascular disease[70]. PIs (particularly ritonavir, lopinavir, and indinavir) and, more recently, INSTIs have been associated with hyperglycemia and development of insulin resistance and diabetes[71, 72, 73]. Early PIs and NRTIs were associated with subcutaneous fat and increased visceral adiposity resulting in lipodystrophy and insulin resistance[74]. While modern first-line ART regimens are felt to have more favorable metabolic profiles, there is increasing concern about excess weight gain related to INSTIs and TAF and potential obesity-related complications. Newer ART, particularly second generation INSTIs (BIC and DTG) and TAF, has been associated with more weight gain than other regimens[75, 76, 77, 78]. Investigation into the cardiometabolic risks associated with such weight gain are ongoing.

Some ART regimens have also been independently associated with increased cardiovascular risk. In particular, ABC has been linked to cardiovascular events which increasingly deters its use in high risk individuals. A large observational study comes from the Data Collection on Adverse Events in Anti-HIV Drugs that demonstrated a two-fold increased risk of myocardial infarction (MI) with ABC use[79]. More recently, the NA-ACCORD, a consortium of HIV cohorts in the US and Canada, evaluated risk of MI in PWH on ABC compared to those on alternate regimens. After adjusting for confounding variables, ABC use within the prior 6 months was associated with an increased risk of both type 1 and type 2 MI[80]. However, it remains up to the discretion of the clinician to assess the individual patient risk of MI compared to the potential benefit of ABC-based therapy. Beyond selecting ART with a favorable cardiovascular profile, mitigating cardiovascular risk with statin therapy presents unique challenges in PWH. Cardiovascular risk assessment tools for the general population underestimate risk for PWH[81, 82, 83, 84]. Guidelines for when to start statin therapy in PWH are extrapolated from the recommendations for the general population but may be expanded as new data becomes available from the ongoing Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study[64]. When initiating statin therapy, providers must be cognizant that statins and some antiretrovirals are metabolized via the CYP system and assess for drug-drug interactions. PIs and pharmacokinetic boosters are at highest risk of interaction with statins. With these regimens, simvastatin and lovastatin should to be avoided; atorvastatin, pravastatin and rosuvastatin may need dose reductions; and pitavastatin may be used without restriction[85].

5.4 Special considerations for women with HIV

Prior to starting ART, healthcare providers and women of childbearing age with HIV should discuss her reproductive goals. For women who are or desire pregnancy, special consideration must be taken to select ART that is safe and effective for both the mother and her child. Poor HIV control is associated with poor outcomes for the mother and increased risk of perinatal transmission of HIV[86]. Unfortunately, the pharmacokinetic and safety of ART during pregnancy remain understudied.. Physiologic changes during pregnancy can affect ART absorption, distribution, metabolism, and excretion[88]. Pregnant women

experience decreased gastrointestinal motility due to progesterone and may alter their food intake due to nausea or vomiting resulting in decreased absorption of ART and other medications. During pregnancy plasma volume expands thereby diluting plasma proteins and leading to increased free drug levels and clearance[89]. Increase cardiac output and glomerular filtration rate lead to increased renal elimination of medication. In addition, pregnancy can differentially increase or decrease drug metabolism via CYP enzymes[90].

For ART-naïve women, only RAL +TDF/FTC is considered preferred in both the DHHS Adult and Perinatal guidelines[10, 87]. Women who are virally suppressed on ART at the time of pregnancy planning or conception should remain on their ART regimen with few exceptions. TAF is not recommended in this population due to insufficient data regarding its use during pregnancy[87]. Recently, concern has been raised about the safety of DTG at the time of conception and during the first trimester in pregnant women with HIV. A slightly increased rate of neural tube defects has been identified in infants born to women who started DTG-containing regimens before the time of conception[91]. A multicenter surveillance program in Botswana initially noted a 0.94% rate of neural tube defects in pregnant women with HIV taking DTG since the time of conception. In a follow-up analysis from July 2018, 0.67% (4/596) had NTD compared to 0.12% of infants born to mother on non-DTG based regimens[91]. As of March 2019 in Botswana with a larger sample size, among 1683 deliveries among women on DTG at conception, 5 NTD were identified (0.30%) compared with 15 NTD among 14,792 deliveries (0.10%) in mothers taking any non-dolutegravir ART at conception[92]. In the same surveillance data, there was only 1 NTD among 3849 (0.03%) in which the mother started DTG during pregnancy typically after the first trimester, and 70 among 89,372 (0.08%) among HIV-uninfected mothers. Given this slightly increased risk of NTD among women on DTG at conception, it is important for providers to discuss the potential risks and benefits of available ART options with women considering pregnancy.

Cobicistat is not recommended during pregnancy. Cobicistat's reliance on metabolic inhibition raised concern that metabolic changes in pregnancy might affect its efficacy. Initial case reports of pregnant women treated with elvitegravir/cobicistat containing ART revealed 44% lower cobicistat exposure during pregnancy than in the postpartum period[93]. Subsequently, a multicenter phase IV trial evaluating cobicistat and elvitegravir pharmacokinetics during the second trimester, third trimester, and postpartum period found that elvitegravir exposure was lower during pregnancy than during the postpartum period[94]. In this study, the lowest values were noted during the third trimester. In fact, only 47% of participants in the 2nd trimester and 38% in the 3rd trimester met the target area under the concentration curve (AUC) goal. Similarly, cobicistat exposure was found to be lower during pregnancy than during the postpartum period. Such unfavorable pharmacokinetics preclude use of cobicistat-containing regimens during pregnancy. Presently ritonavir is the preferred boosting agent during pregnancy[87].

Women of childbearing age who do not desire pregnancy should be offered contraceptive counseling as part of routine HIV care. Combined oral contraceptives (COCs) and implanted hormonal contraceptives can be affected by ART leading to ineffective contraception. However, limited data exist to fully characterize the interactions and clinical implications.

Most notable is the interaction of EFV with implanted levonorgestrel in which women on EFV-based regimens with implanted levonorgestrel were shown to have decreased levels of levonorgestrel, a progesterone, and increased rates of contraception failures[95]. Even with addition of a second levonorgestrel implant, this interaction persisted[96]. Boosted PI based regimens can interfere with ethinyl estradiol and lead to decreased levels and increased risk of side effects (e.g., vaginal bleeding), but ultimate impact on pregnancy prevention may be limited. Depot delivery of hormonal contraception utilizing medroxyprogesterone acetate (MPA) leads to higher levels of MPA and hence, has not been shown to be affected by ART. The DHHS perinatal HIV guidelines include Table 3 “Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives” that summarizes the available data and expert recommendations for prescribing hormonal contraceptives with ART[10]. This potential for decreased contraceptive efficacy should prompt clinicians to encourage additional methods of pregnancy prevention, but not prevent prescribing of hormonal contraception.

Among transgender women with HIV, gender-affirming hormonal therapy (HT) may also be impacted by ARVs, but most data has been extrapolated from COCs. Gender affirming hormone therapy usually consists of an androgen blocking agent and an estrogen agent. Spironolactone is the most frequently used anti-androgen medication in the US and no drug interactions with ARVs have been identified[97]. PIs and NNRTIs may decrease levels of circulating estrogen, requiring closer monitoring to achieve a clinically efficacious dose of estrogen. The concern for drug-drug interactions and decreased efficacy of HT may lead to reduced adherence to ARVs in favor of HT if not monitored and addressed by the provider[98].

6. Challenges with ART maintenance

6.1 Maintaining Engagement in Care

Successful ART requires that PWH remain engaged in care and adherent to ART for the remainder of their life. Among adults and adolescents living with HIV in the United Sates in 2015, only 49% were engaged in continuous HIV care and 51% had achieved virologic suppression[99]. Numerous barriers across the HIV care continuum--from intrapersonal patient obstacles to issues of national health policy--pose challenges for engagement in and adherence to continued HIV therapy[100, 101].

Psychosocial factors are a significant contributor to ART nonadherence. Effective management of HIV must address social barriers such as stigma[102, 103], loneliness[104, 105], unstable housing[106], and intimate partner violence[107] that can contribute to decreased medication adherence. Intensive social work and case management support can help to identify and direct appropriate interventions to facilitate continuous HIV care, such as housing, transportation, insurance coverage, and mental health treatment[108, 109]. For PWH who face significant financial and structural barriers, more intensive outreach and peer navigator interventions may help to determine needed supportive services[110, 111].

HIV care providers must also actively address and manage comorbidities that affect medication adherence. Rates of mental health disorders, neurocognitive impairment, and

substance abuse are increased among PWH compared to the general population[59, 112, 113]. Ongoing depressive symptoms adversely affect engagement in HIV care[114, 115]. Integrated treatment of opioid dependence and HIV has been shown to increase number of visits, ART initiation, and rates of virologic suppression[116, 117]. Providers offering pharmacologic therapies for opioid dependence and mood disorders in PWH must be cognizant of potential drug interactions with ART. For example, all ritonavir-boosted PIs as well as efavirenz decrease methadone's AUC, so providers must adjust methadone dosing and/or monitor patients for signs of opioid withdrawal with co-administration of these mediations [10].

Among PWH already established on virally suppressive ART, some regimen switches may be considered to improve adherence, decrease medication side effects and long-term toxicities, or avoid drug-drug interactions. To maintain viral suppression, it is imperative to consider any prior resistance mutations as well as the new regimen's barrier to resistance when making changes in ART. Within class switches to an agent with a similar barrier to resistance--such as changing TDF to TAF to reduce bone and renal toxicity—is a reasonable strategy. Similarly, between class switches to an agent with a similar barrier to resistance-such as changing a boosted PI to DTG—are also effective. However, switching to an agent with a lower barrier to resistance either in the same (e.g., DTG to RAL) or a different (e.g., DTG to RPV) class should only be considered if there has not been any prior resistance noted[10].

Maximizing ART convenience can promote adherence and is a common reason for switching regimens. Food requirements, excess pill burden, and higher dosing frequencies can contribute to treatment-fatigue. Single tablet regimens (STRs) can increase adherence and virologic suppression as well as decrease rates of discontinuation and laboratory abnormalities[118]. There are a growing number of STRs available. However, for certain populations, like individuals on hemodialysis, fixed dose combinations may not be appropriate. One case series has demonstrated the safety and efficacy of a single tablet regimen with DTG/ABC/3TC in patients with HIV and ESRD on hemodialysis but has not been studied on a larger scale[119].

Virologic failure (or the inability to maintain viral suppression below 200 copies/mL) also warrants re-evaluation of the individual's ART regimen. Prior to switching therapies, providers and PWH should address and intervene on any factors that may limit adherence to and efficacy of the current regimen, such as improper dosing, cost, or drug-drug interactions. In the setting of virologic failure, resistance testing should be performed—including assessment for integrase resistance if prior ART included an INSTI. When selecting a new ART regimen, current and historical resistance must be considered. For PWH with virologic failure, switch regimens must contain at least 2 but ideally 3 active drugs[10]. In some cases, there may still be active drug options in the same ART classes as the failing regimen that has a higher barrier to resistance. For example, in the setting of a K103N mutation conferring resistance to EFV, other NNRTIs such as doravirine, rilpivirine, and etravirine may still retain activity. In the setting of multidrug resistant HIV, providers may consider addition of an active drug with a different mechanism of action, such as a CCR5 antagonist, fusion inhibitor, or the recently approved post-attachment inhibitor ibalizumab[120]. When

constructing a salvage regimen for PWH with extensive drug resistance, consultation with an HIV expert is recommended.

6.2 Challenges in a young adult population

For adolescents living with HIV, the transition to adult care represents a particularly vulnerable period for retention in care and virologic suppression. In 2017, youth aged 13 to 24 years old accounted for 21% of new HIV diagnoses in the United States. Moreover, there are a growing number of adolescent and young adult long-term survivors of perinatal HIV infection[121]. ART adherence can be a particular challenge for adolescents with either recently or perinatally acquired HIV infection[122, 123]. Furthermore, teens and young adults living with HIV have poorer virologic outcomes and follow-up rates[124]. As such, HIV clinics focused on adult care must be attuned to the specific needs of adolescents transitioning into their care.

While the general factors that affect retention in care and ART adherence in all PWH apply to adolescents and young adults living with HIV, such challenges can be magnified in this population. Youth transitioning to adult HIV care may be more likely to have gaps in health insurance, concerns about disclosure of their HIV status if they remain on their parents' insurance, and less experience navigating complex health systems[125]. Many young PWH also have decreased social support[126] and experience high rates of mood disorders[127] that can impact adherence and follow-up. Therefore, comprehensive clinic models that are easily navigable, offer intensive mental health and social support, and include HIV providers with significant experience in care transitions can improve outcomes for young PWH.

Moreover, adolescents tend to be less risk averse and are still developing concrete thinking skills which can diminish adherence to ART or any chronic medication. To prevent development of resistance, ART may sometimes be deferred until adherence is more likely and the most potent and easily dosed regimen should be selected[10]. However, long-term survivors of perinatal infection are often highly ART experienced, with higher likelihood of harboring HIV resistance mutations, and tend to be on more complex regimens[128]. User-friendly, inconspicuous support systems such as apps, reminder calls, and even pill boxes can help to bolster ART adherence among adolescent and young adults living with HIV[129, 130].

6.3 Challenges in an aging population

Management of HIV in older adults poses a special set of challenges. With successful ART, PWH are living longer. In addition, HIV risk persists in older ages. In 2015, adults over the age of 50 accounted for 47% of known as well as 17% of new HIV diagnoses in the United States. Older patients tend to present with lower CD4 counts at time of diagnosis and have steeper declines in CD4 count over time[131, 132, 133]. With initiation of ART, elderly PWH tend to have improved adherence compared with younger adults but have decrease immune recovery compared to younger patients [134, 135, 136]. Due to their depressed immune recovery and increased risk of other adverse outcomes, older PWH benefit the most from early initiation of ART[137]. Despite increased immunosenescence, older patients have

a virologic response similar to that of younger individuals on ART and, in some studies, even higher rates of viral suppression presumably from improved adherence rates[136, 138].

While initial ART recommendations remain the same for older patients, providers must be cognizant of this population's specific clinical characteristics. Older individuals are more likely to have comorbidities--such as decreased renal function, cardiovascular disease, or reduced bone mineral density—that may impact choice of ART. For example, dosage adjustments of NRTIs may be required for patients with kidney disease. Similarly, associations between ABC and increased risk of cardiovascular events may lend caution to its use in older patients, who may already have heightened cardiovascular disease risks[80]. Studies of the pharmacokinetics, efficacy, and adverse effects of ART in the elderly have been limited. Following initiation of ART, older patients should be monitored for development of adverse drug effects.

Older adults living with chronic HIV infection experience both earlier onset and higher rates of chronic non-infectious aging-related comorbidities than the general population[139, 140, 141]. The mechanisms underlying these differences are not fully understood but have been attributed to chronic inflammation and immune activation, ART toxicities, and increased prevalence of high-risk behaviors (e.g., smoking) among PWH. Development of additional comorbidities may prompt changes to ART to minimize toxicity. If a patient on a TDF-based regimen develops osteoporosis, for example, that individual and their provider may consider switching to TAF or a NRTI-sparing regimen. In addition, older PWH with multiple comorbidities are at increased risk for polypharmacy[142, 143]. Such individuals must be carefully monitored for potential drug-drug interactions.

Among other comorbidities, persons aging with HIV are at increased risk for geriatric syndromes such as frailty and cognitive impairment[144, 145, 146]. As a result, this population is particularly vulnerable to poor health outcomes such as disability, reduced quality of life, and social isolation[147, 148, 149, 150]. These age-related comorbidities can also contribute to non-adherence. Similarly, depression, social isolation and neurocognitive impairment can all decrease adherence and engagement in HIV care[151, 152]. Increasing pill burden and, as a result, medication costs, may decrease adherence and contribute to virologic failure in older PWH. Attention to these complex, age-related issues is essential not just to maintain virologic control but also to maximize quality of life for PWH across the age continuum.

7. Future of ART

Current ART regimens are now safer, more convenient, and more efficacious than ever. First line ART with INSTI-containing three-drug regimens are well-tolerated, highly effective with a high resistance barrier, and often available as single tablet regimens. Novel ART agents and strategies offer the promise of further reductions in medication toxicity, more convenient administration, and improved efficacy against resistant virus.

7.1 Dual ART

There is growing evidence that dual therapy is efficacious and may reduce cost and drug toxicity. Some guidelines include DTG + 3TC, DRV/r + RAL twice daily and DRV/r+ 3TC as potential initial ART in special situations, such as when tenofovir or abacavir cannot be used[10]. DRV/r +RAL is further restricted to patients with VL < 100,000 copies/mL and CD4 > 200 cells/μL.

There is greater evidence supporting a switch to dual therapy following virologic suppression with three-drug ART. SWORD-1 and 2 demonstrated that a once-daily combination of DTG plus RPV maintained virologic suppression in greater than 95% of participants switched off of their previous combination ART[153]. DTG/RPV is now available as a co-formulated tablet. Dual therapy with a PI/r and emtricitabine also has growing supportive evidence[154, 155, 156, 157]. However, PI-based dual therapy has had limited uptake due to its propensity for drug interactions and adverse effects, such as metabolic derangements.

Dual therapy with a boosted-PI plus an INSTI or DTG plus 3TC also has some supporting evidence as switch therapy but are still not recommended in guidelines. Small studies have shown that viral suppression was maintained in 97% of patients switched to DRV/R plus DTG[158, 159]. The combination of DTG plus 3TC maintained virologic suppression in the LAMIDOL and ASPIRE studies[160]. Recently, GEMINI 1 and GEMINI 2 demonstrated non-inferiority of DTG + 3TC to DTG + TDF/FTC as initial ART[161]. In addition, DTG/3TC is also now available as a co-formulated tablet.

Though dual therapy shows increasing promise and offers some potential advantages, significant limitations constrain its use. Dual regimens all lack the two NRTIs recommended for treatment of HIV and HBV co-infection and are therefore contraindicated in this population. Furthermore, dual regimens have not been investigated in the setting of tuberculosis co-infection, pregnancy, and renal disease. The lack of data in these key populations limits dual regimens' widespread uptake.

7.2 Long-acting ART

While dual regimens may decrease toxicity and cost, other novel therapies offer innovative delivery techniques to improve adherence. Long-acting antiretroviral therapies including parenteral agents, implants, and patches may offer promising treatment alternatives for PWH who have difficulty adhering to a daily pill-based regimen. Long-acting injectable nanoformulated antiretrovirals are farthest along in clinical trials. The Phase II LATTE-2 trial showed that after a 20 week oral lead in, an all injectable regimen of cabotegravir, a novel INSTI, and rilpivirine monthly or every 2 months was as effective as three-drug oral ART at maintaining viral suppression[162]. Phase III clinical trials are ongoing to evaluate this combination as initial ART (FLAIR), switch therapy for PWH with viral suppression on an oral ART regimen (ATLAS), and in PWH with a history of poor adherence to ART and poorly controlled HIV (LATITUDE/ACTG A5359). Development of additional new long-acting injectable antiretrovirals is also underway. The novel NNRTI, elsulfavirine (VM1500A), is distinguished by its tolerability and long half-life. Preclinical

pharmacokinetic studies have shown the potential to develop VM1500A as long-acting injectable agent and a Phase 1b trial investigating its weekly dosing is underway (ClinicalTrials.gov NCT03730311).Bichko V, Rogovoy B, Koryakova A, et al. Pre-clinical pharmacokinetics of elsufavirine/VM1500A long acting injectable formulations. International Antiviral Society-USA. 2017. Poster WEPEA0190.. A new long-acting fusion inhibitor, albuvirtide, has been approved in China and is well-tolerated[163]. There are ongoing efforts to develop a subcutaneous formulation of albuviritide that would allow self-administration every 2–4 weeks.

Broadly neutralizing antibodies (bNAbs) offer another promising new class of long-acting parental therapy for both HIV treatment and prevention[164, 165]. HIV bNAbs were originally isolated from individuals with high levels of anti-HIV neutralizing activity and target antigens on the HIV external membrane glycoprotein 120 (gp120). Early clinical studies have shown that bNAbs can reduce viral load, stimulate immune response to HIV and HIV-infected cells, and are well-tolerated[166, 167]. Clinical trials are now underway to test combinations of bNAbs as well as bNAbs combined with a long-acting antiretroviral such as albuvirtide (3BNC117) which is being investigated as long-acting maintenance therapy in ClinicalTrials.gov NCT03719664.

Antiretroviral implants and patches could offer alternative long-acting treatment approaches. In contrast to parenteral therapies, implants and patches would not require more clinic visits for infusions and therefore may be more applicable to resource poor settings. A novel nucleoside reverse transcriptase translocation inhibitor (NRTTI), MK 8591 (islatravir), has a prolonged half-life of 150 to 160 hours and potent activity against HIV-1, -2 , as well as multidrug resistant strains[168]. As a result of its these properties, MK 8591 has been formulated in a drug-eluting implant[169] and is an attractive candidate for long-acting pre-exposure prophylaxis (PrEP) and as well as HIV treatment. Other novel drug delivery technology, including microneedle patches for transdermal delivery[170] and biodegradable implants[171], may offer promising future long-acting treatment strategies as well.

7.3 The ART Pipeline

Entirely new classes of antiretrovirals are also under development and may offer more therapeutic options especially for highly treatment experienced PWH. The first CD4 attachment inhibitor, fostemsavir, acts by binding to HIV envelope glycoprotein 120. It is currently under investigation in the Phase III BRIGHTE study for heavily treatment experienced PWH with multidrug resistance (ClinicalTrials.gov NCT02362503). Similarly, the novel class of capsid inhibitors have been shown to be potent against HIV-1 at both early and late stages of viral replication in vitro[174]. These agents, which include GS-CA1 and its modified version GS-6207, interfere with capsid disassembly and render virions non-infectious. Moreover, GS-6207 has unique pharmacokinetic properties that may allow for long-acting subcutaneous administration and is currently in Phase I trials (ClinicalTrials.gov NCT03739866). Finally, ABX464 is an orally available small molecule in the novel class of Rev inhibitors and blocks viral replication by preventing the export of viral RNA from the nucleus to the cytoplasm in HIV-infected cells. By interfering with the HIV protein Rev which is essential for this transport out of the nucleus, this drug prevents production of new

virus and also triggers immune activation to eliminate HIV-infected cells. As such, this agent is thought to reduce the HIV reservoir and has the potent to be part of functional cure strategies[175].

8. Expert Opinion

Effective ART has transformed HIV from a uniformly fatal illness to a chronic, manageable condition. On modern ART, a young adult in North America diagnosed with HIV today has a life expectancy nearing that of the general population[1]. Such effective treatment also prevents the spread of HIV and is crucial for ending the epidemic[14, 15, 176]. However, attaining these benefits of ART currently requires that PWH be adherent to lifelong, daily ART. While modern ART is increasingly safe, effective, and convenient, challenges persist in initiating and maintaining ART throughout adulthood.

When selecting initial ART, an individual's coexisting medical, social and personal factors must be considered. While several first-line single table regimens are now available, these once daily regimens may be contraindicated in persons with certain comorbidities. In particular, fixed dose combination pills may not be appropriate for those with renal disease or during pregnancy. As a result, some persons with HIV must take less convenient multi-tablet regimens, which are associated with increased risk of non-adherence.

Maintaining ART across changing life conditions often proves more challenging than initiating therapy itself. For women living with HIV, the risks and benefits of various antiretrovirals change across their reproductive years. ART can have significant drug interactions with hormonal contraception. Many first-line ART regimens have safety and efficacy concerns during pregnancy. Therefore, it is imperative that providers continually discuss reproductive goals with all PWH and especially those who are able to become pregnant to ensure that their ART is concordant with their parenting desires[177]. In addition, as PWH live longer on effective ART, providers must be cognizant of therapeutic issues in the growing population of persons aging with HIV. Polypharmacy, medical comorbidities, cognitive difficulties and social isolation can all increase with age and lead to greater drug toxicity and difficulties with adherence. Moreover, for PWH of all ages and genders, providers must watch for and actively manage factors that may lead to ART non-adherence, such as pill burden, ART side effects, cost of medications, homelessness, intimate partner violence, stigma, opiate addiction, and mental health concerns. Furthermore, providers must watch for virologic failure and emergence of antiretroviral resistance that may require ART modification.

Emerging therapies and novel approaches to ART delivery will address many of these challenges but may also raise new complications. Long-acting ART, administered as injections, patches or implants, has the potential to increase convenience and adherence. However, these therapies may be more expensive and place increased burden on clinics and PWH. In the event of a missed injection, for example, such long-acting administrations can have months-long low-level drug concentrations that could lead to drug resistance. Dual therapy has the potential to decrease ART toxicity and cost. But currently two-drug ART regimens can only safely be used in a subset of PWH. Other therapies under development

may offer new antiretrovirals in existing and novel drug classes that may further combat continued resistance, increase efficacy, and, hopefully, bring the field closer to functional cure.

Continued HIV research must address ART in populations historically underrepresented in clinical trials for whom therapeutic disparities persist. Further studies are needed to better understand potential complications in and improve ART for female, aging, medically complex, and transgender PWH. Over the last 4 decades, advances in ART have revolutionized HIV care. Until HIV cure arrives, future research must continue to improve the efficacy, safety, convenience, and equitability of ART for all persons living with HIV.

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Papers of particular interest have been highlighted as:

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** of outstanding interest

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Article Highlights:

- Antiretroviral therapy (ART) has transformed HIV into a chronic, manageable illness. Virally suppressive ART extends the life-expectancy of PWH to near that of the general population but requires life-long adherence.
- Selection of an initial ART regimen requires multiple considerations including baseline resistance, co-infections, and co-morbidities.
- ART remains understudied in women and during pregnancy. Women living with HIV and their providers must discuss her reproductive goals to ensure safe and effective ART.
- Multidisciplinary approaches are essential for maintaining engagement in care and viral suppression across the adult lifespan of PWH.
- Emerging ART—including dual therapy and long-acting agents—offer the promise of safer, more convenient, and more efficacious treatments.

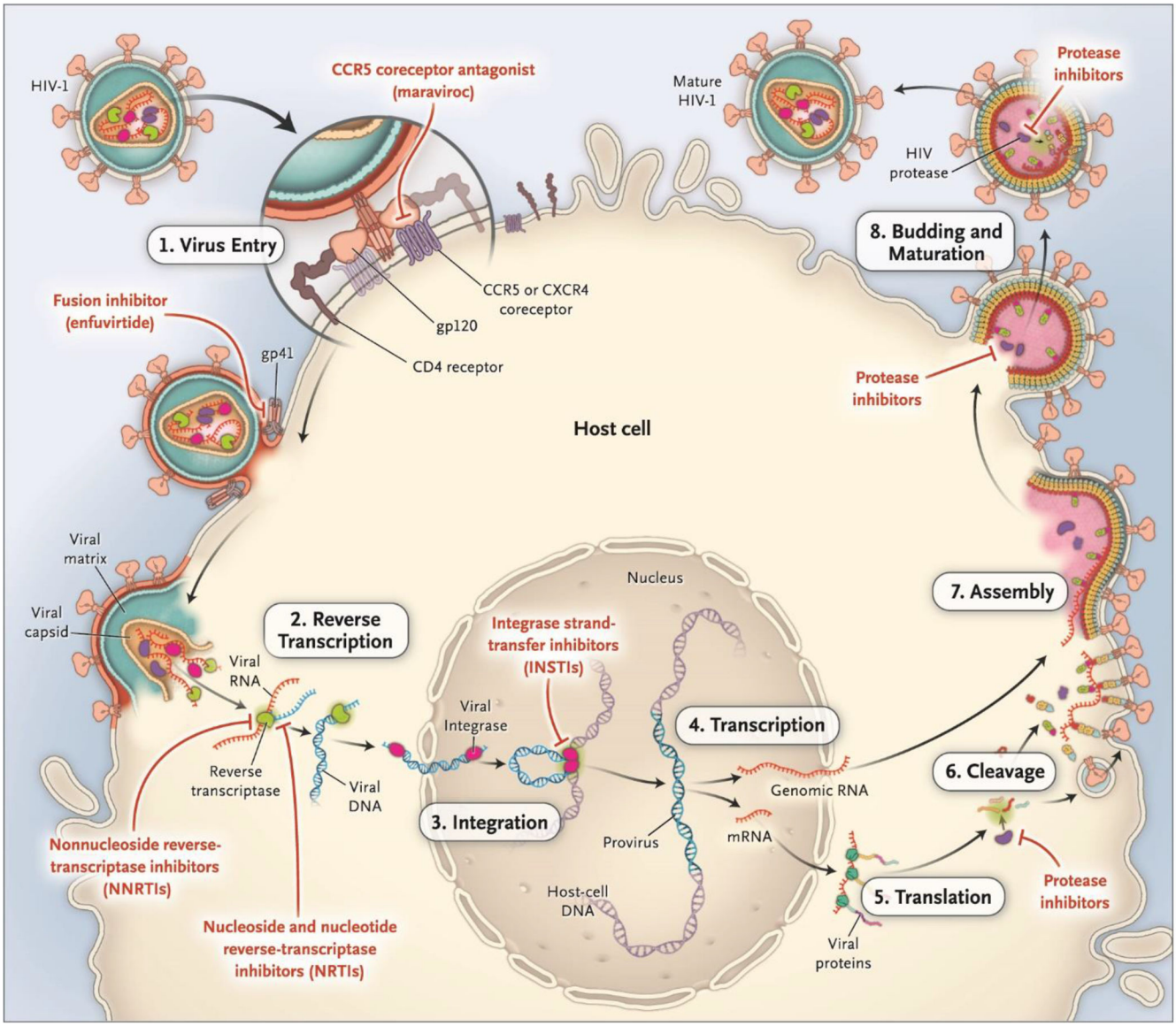

Figure 1.

Reproductive Cycle of Human Immunodeficiency Virus and Sites of Action of the Major Classes of Antiretroviral Medications.

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