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Why Everyone (Almost) with Human Immunodeficiency Virus Needs to Be on Treatment:

A Review of the Critical Data

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INTRODUCTION: MOVING BEYOND CD4 COUNT THRESHOLDS

The introduction of potent combination antiretroviral therapy (ART) in the mid-1990s changed the landscape of human immunodeficiency virus (HIV), bringing marked improvements in morbidity and mortality.^{1,2} The designation of these regimens as highly active antiretroviral therapy [HAART], represented a shift in how these medications were perceived. ART had evolved from pills that may slow the devastating progress of HIV to regimens that could more reliably and sustainably suppress viral replication and restore a person to health. The development of plasma HIV viral load assays allowed clinicians and people with HIV (PWH) to monitor this progress. In the present day, more than 20 years after the introduction of effective ART, the term ART is routinely used and reflects the current state of the science: all ART is highly active, potent, durable, and generally well tolerated (Fig. 1A).

Despite these advances, over the 20 years following the introduction of effective therapy, guidelines remained conflicted on when to initiate ART. Early regimens, following the introduction of protease inhibitors and combination ART, were expensive and carried the risk of adverse effects and resistance caused by incomplete viral suppression. From 1998 until 2000, the US Department of Health and Human Services guidelines recommended that all PWH be offered treatment, but these recommendations were amended, reflecting uncertainty about the optimal use of these powerful and often toxic medications. CD4 thresholds became the focus of efforts to maximize the benefits of ART while minimizing associated risks. Guidelines agreed that PWH with a CD4 threshold less than 200 cells/mm³ should receive ART. This threshold was then increased to 350 cells/mm³ from 2006 to 2009, then to 500 cells/mm³ from 2009 to 2013.

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Since 2014, a consensus of landmark studies has justified starting ART regardless of CD4 count and, in many cases, before getting the results of this test. The evidence for immediate and universal ART is strong, clearly showing individual and population-level benefits and is supported by all major guidelines groups (Table 1). Altogether, improvements in ART and recognition of its clinical and epidemiologic benefits justify near-universal ART (Fig. 1), preferably as soon after the diagnosis of HIV as possible.

This article reviews the evidence supporting near-universal ART regardless of CD4 count and the shift in practice to ART initiation immediately following HIV diagnosis. It provides case-based discussions to explore the evidence behind the current recommendation for ART for all PWH and discusses specific situations showing the rare scenarios in which ART initiation may be delayed.

NEW HUMAN IMMUNODEFICIENCY VIRUS DIAGNOSIS

Case 1: a 21-year-old male college student was diagnosed with HIV when he developed a rash and presented to student health. He was diagnosed concomitantly with secondary syphilis (rapid plasma reagin 1:256) and treated at the local county health department. His most recent negative HIV test was 6 months before HIV diagnosis. Apart from the rash, now resolved, he is asymptomatic. His CD4 is 579 cells/mm³ (29%), HIV viral load 180,000 copies/μL. He is still on his parents' insurance and worried about medication cost and accidental disclosure. His partner, who accompanies him, is confirmed to be HIV negative.

Clinical Benefits

Initiation of ART as soon as possible after confirmation of HIV diagnosis is beneficial for almost all PWH, with the exception of those with cryptococcal meningitis or tuberculosis (see case 5). Some of the most convincing evidence for this recommendation comes from 2 large clinical trials (Strategic Timing of Antiretroviral Therapy [START] and TEMPRANO), which clearly showed a reduced risk of both AIDS and non-AIDS clinical events among participants who initiated ART at CD4 greater than 500 cells/mm³ or higher (see Fig. 1B).^{7,8} Table 2 summarizes these and other key trials and cohort studies that have shaped current practice.

In considering this patient and his concerns regarding initiating ART, note that, in addition to preventing the progression of HIV, ART reduces HIV-associated immune activation and inflammation, helping to reduce risk of vascular and end-organ damage and malignancy.⁸ For a young, asymptomatic patient this may be a less compelling consideration, but ART initiation greatly decreases his risk of further complications and associated hospitalizations.¹⁴ ART initiation is likely to increase his life expectancy; in a recent study, disparity between life expectancy for persons with HIV and without HIV in the United States was reduced from 13.1 to 7.9 years by ART initiation at CD4 greater than or equal to 500 cells/mm³.¹⁵ Another important benefit of ART for this patient is prevention of transmission of HIV to his current partner or others if he remains virologically suppressed on ART.^{13,16} Individual patient readiness to initiate ART is of utmost importance, but every effort should be made to start ART as soon as is feasible. When possible, leveraging support resources within the clinic and community is critical in ensuring ongoing engagement

in HIV care. This case also shows the importance of screening for sexually transmitted infections, including viral hepatitis, at the time of HIV testing and at appropriate intervals thereafter.

Medication Cost and Access

This patient's concern about medication cost and insurance implications is common. ART is expensive, with manufacturer wholesale pricing for a typical branded combination regimen averaging more than \$3000/mo⁵. Most private and federal plans offer full or partial coverage of many acceptable regimens and patient copays may vary depending on plans. Many PWH qualify for resources such as pharmaceutical company copay assistance programs or Ryan White programs such as the AIDS Drug Assistance Program. Team-based support, including nurses, social workers, case managers, and pharmacists, for PWH initiating ART is invaluable in navigating the specific challenges associated with ART initiation and adherence. For this patient, options may include accessing a manufacturer assistance program, seeking independent insurance, or considering participation in a research study if available.

Improvements in Antiretroviral Therapy Tolerability and Efficacy

For most PWH newly initiating ART, a typical regimen consists of a combination of agents from at least 2 classes, usually nucleoside or nucleotide reverse transcriptase inhibitors and integrase strand transfer inhibitors.³ The pill burden for a new regimen is 1 to 2 pills taken daily, compared with the numerous pills, prominent side effects, and frequent dosing that were hallmarks of earlier generations of ART. Side effects of modern ART, most commonly headache and nausea, generally diminish after the first few weeks of therapy. The integrase strand transfer inhibitor dolutegravir may cause mild neuropsychiatric side effects, including insomnia, but is well tolerated in most patients and rarely requires discontinuation because of side effects. The authors advise involving the patient in decision making in selecting the optimal ART regimen and establishing close follow-up to monitor for any side effects, concerns, or barriers to accessing ART. PWH should be educated regarding the risks of self-discontinuing or modifying ART, including rebound of hepatitis B (if applicable) and concern for development of resistance with inconsistent administration.

DIAGNOSIS DURING ACUTE HUMAN IMMUNODEFICIENCY VIRUS INFECTION: THE CASE FOR URGENT ANTIRETROVIRAL THERAPY INITIATION

Case 2: a 44-year-old previously healthy man presented for evaluation and management of newly diagnosed HIV. He was seen at an emergency department in a nearby town after the acute onset of severe headache, fever of 38.9°C (102°F), arthralgias, loose stools, tremor, malaise, and diaphoresis. He was given supportive care with intravenous fluids and discharged home. His symptoms persisted and he developed a painful pharyngitis. Three days after onset of these symptoms he presented to an urgent care clinic and was prescribed amoxicillin and a brief prednisone taper after rapid testing for HIV, *Streptococcus*, influenza, and mononucleosis were negative. Nine days after his initial symptom onset he was seen

by his primary care physician, who noted diffuse lymphadenopathy, lymphopenia (absolute lymphocyte count <1000 cells/mm³), thrombocytopenia (70,000 platelets/mm³), and an increased aspartate aminotransferase (AST) of 78 IU/L. Screening HIV antigen/antibody (Ag/Ab) testing was positive, but Multispot was negative. A confirmatory HIV viral load was 750,000 copies/ μ L, consistent with acute HIV.

Acute or early HIV infection (AHI) is generally defined as the weeks to months following HIV infection before development of antibodies to HIV.¹⁷ Most AHI is symptomatic, although symptoms may be nonspecific and persons with AHI may not seek medical care for their symptoms, or their disclosed history may not prompt HIV testing by medical providers. The increased use of fourth-generation HIV Ag/Ab testing allows a greater proportion of new HIV diagnoses to be identified during the acute period. The importance of HIV diagnosis during AHI is underscored by the increased transmission potential caused by the typically high viral load burden.¹⁷ A study in North Carolina identified AHI using pooled nucleic acid amplification for antibody-negative samples and individual HIV RNA for antibody-indeterminate samples found that 3.4% of individuals diagnosed with HIV during the study time period (2003–2012) had AHI.¹⁸

Benefit of Antiretroviral Therapy During Acute Human Immunodeficiency Virus Infection: Curbing Human Immunodeficiency Virus Progression and Inflammation

Symptomatic presentation with AHI has been associated with high levels of HIV viremia and more rapid progression of disease, highlighting the importance of immediate ART initiation during this period (Box 1).¹⁹ The robust viral replication that occurs in AHI triggers widespread immune cell activation, increases the viral reservoir, and has longer-term implications for disease progression.^{20,21} Early ART decreases CD4 and CD8+ T-cell activation and results in smaller HIV proviral DNA and RNA reservoir size.^{20,21} CD4 counts typically decline markedly in the setting of AHI and early ART may increase the trajectory and extent of CD4 count recovery, particularly if initiated as close to seroconversion as is possible.^{17,22} However, studies to date indicate that ART does attenuate but not fully resolve chronic inflammation.²³ Very early immune damage by HIV is durable and potential irreversible in inflammation biomarker studies (RV254/SEARCH010) and early initiation does not resolve the chronic inflammation associated with all-cause morbidity and mortality risk in treated HIV infection.²³ Nonetheless, early ART initiation attenuates inflammation more than when ART is initiated in chronic HIV infection. However, more research is needed to determine whether reduction in viral reservoir correlates with improvement in end-organ function or other clinical benefits.²⁴

Reduction of Latent Viral Reservoir

Early ART limits the size of HIV reservoirs compared with later treatment and may be the necessary foundation for reservoir containment.²¹ The size of the viral reservoir during chronic HIV infection is established in early AHI with a set-point viral load reached within the first 2 months.²¹ Infection persists in long-lived memory CD4+ T cells in peripheral blood and mononuclear cells in tissues. Initiation of ART during AHI reduces proviral DNA early in infection and with marked reduction in HIV DNA set-point; further, HIV DNA is persistently reduced with continuation of long-term ART.²⁵ The semen reservoir

is established later and more gradually than the blood reservoir; however, the semen viral reservoir is reduced during early ART treatment, thereby reducing the high transmission risk during AHI.²⁶ The clinical impact of viral load reduction through ART and behavior change has been shown among 88 MSM with AHI in Thailand, where transmission over the first year following infection was estimated to be reduced by 89%.²⁷

RAPID ANTIRETROVIRAL THERAPY INITIATION AT HUMAN IMMUNODEFICIENCY VIRUS DIAGNOSIS

Rapid ART is defined as initiation within 14 days of confirmed HIV diagnosis and is a component of a growing movement to facilitate streamlined entry into HIV care with same-day ART initiation.^{28–30} There is mounting evidence indicating the benefits of early ART initiation, including initiation of ART on the same day the diagnosis of HIV is confirmed (Box 2). Although multiple barriers to initiating rapid ART exist (Box 3), persons with no contraindication to early ART should be offered rapid ART initiation. World Health Organization guidelines now recommend ART initiation as soon as possible after an HIV diagnosis is confirmed.³¹

A meta-analysis of 22 studies, including 2 randomized controlled trials (in Haiti and South Africa), 2 cluster randomized trials (in Uganda and Lesotho), and 11 observational studies (in 8 countries including the United States), showed that accelerated ART, including ART started on the day of diagnosis, can lead to improved clinical outcomes.³⁰ In Haiti, same-day HIV testing and ART initiation were assessed in a randomized controlled trial for PWH with CD4 less than 500 cells/mm³ and compared with standard ART initiation (approximately 3 weeks after testing).²⁸ The study found improvements in retention in care with virologic suppression at 12 months (53% vs 44% in the standard group had RNA<50 copies/μL at 12 months).

Two clinic-based studies in the United States show feasibility and reductions in time to virologic suppression.^{32,33} In San Francisco, a clinic-based cohort prioritized same-day ART for PWH diagnosed during acute/recent infection or for those with CD4 less than 200 cells/mm³.³² The study was successful in starting ART within 24 hours for more than 90% of eligible PWH and found reductions in time to virologic suppression compared with nonintervention PWH. The feasibility and effectiveness of rapid ART start was also shown in a clinical cohort of mostly uninsured and underinsured PWH in Atlanta.³³ This study found reductions in time to viral suppression and time to first provider visit.³³ Other studies also found shorter time to viral suppression among an observational cohort in San Diego with initiation of ART within 30 days of diagnosis; immediate ART was offered at first intake visit.³⁴

PUBLIC HEALTH BENEFITS OF IMMEDIATE ANTIRETROVIRAL THERAPY: TREATMENT AS PREVENTION

Numerous studies have shown that ART markedly reduces risk of HIV transmission from PWH to their partners, eliminating risk of sexual transmission in the setting of durable

viral suppression (see Fig. 1C).^{13,36–39} Widespread recognition of this concept, known as treatment as prevention (TasP), occurred in 2011 with the early release of data from HPTN 052, a large study of serodiscordant, mostly heterosexual couples in 9 countries.¹³ The HIV-positive partners in the study were asymptomatic, with CD4 count of 350 to 550 cells/mm³, and randomized to start ART at time of enrollment versus delaying ART. Early ART reduced rates of sexual transmission of HIV to the uninfected partner by 96%.¹³ No phylogenetically linked incident infections were observed when the HIV-positive partners were virologically suppressed (1 transmission event occurred before virologic suppression of the infected partner).¹³ The Partners of People on ART-A New Evaluation of the Risks (PARTNER), PARTNER2, and Opposites Attract studies reported strong evidence that TasP is effective among men who have sex with men, with zero linked HIV transmission events among couples in any of these studies.^{40–42} Together, these data have formed the basis for the compelling Undetectable = Untransmittable (U=U) campaign, which has gained worldwide support since 2016 and is an important tool in counseling PWH and their partners and reducing stigma associated with HIV.⁴³

Despite this galvanizing progress, challenges to implementing universal TasP remain, particularly in areas with highly prevalent and incident HIV. A population-based cohort in a high-HIV-prevalence (30%) district of KwaZulu-Natal, South Africa, showed substantial reductions in household HIV incidence among PWH with immediate eligibility to receive ART (CD4<350 cells/mm³).⁴⁴ However, in the ANRS (French National Agency for Research on AIDS) 12249 TasP trial, performed in the same district, there was no significant difference in cumulative incidence by arms, a finding attributed to low linkage to HIV care and subsequent limited increase in ART coverage.⁴⁵ Further analysis of population dynamics in this study revealed that the high incidence of HIV essentially outpaced the benefit of suppressive ART in this population.⁴⁶ Although TasP is an immensely promising tool, these results highlight the need for robust linkage and retention efforts for all PWH.

ANTIRETROVIRAL THERAPY AND SPECIAL POPULATIONS

Pregnancy

Case 3: a 24-year-old woman presents after a new diagnosis of HIV in the context of a prenatal visit. Her partner is HIV positive and she is not sure whether he is on ART. Her last HIV test was 2 years before the current visit. This pregnancy is her first. Ultrasonography reveals a fetus at 12 weeks' gestational age. Laboratory results show CD4 446 cells/mm³ (36%), and HIV RNA 140,000 copies/μL. She is committed to following medical advice to maximize the chances for a healthy baby but is also concerned about toxicity of ART for the fetus.

Reduction of Perinatal Human Immunodeficiency Virus Transmission

Initiation of ART in pregnant women carries particular urgency both to ensure the health of the mother and to prevent perinatal transmission of HIV. Worldwide, enormous strides have been made in reducing mother-to-child transmission of HIV, largely attributable to effective combination ART and maternal virologic suppression.⁴⁷ Although viral suppression at the time of delivery is an important focus of monitoring during pregnancy, several studies have

also shown that earlier ART initiation, optimally before conception, further reduces risk of transmission.^{48,49}

Antiretroviral Therapy and the Developing Fetus

This patient's concern regarding the toxicity of ART for a developing fetus is common and an important consideration. There are a variety of preferred (well-validated) and acceptable (less well-studied, particularly with regard to pharmacokinetics) ART regimens for pregnant women with HIV, and almost any ART regimen is preferred to no ART.⁵⁰ Uncontrolled maternal HIV presents the greatest risk to the fetus and is associated with adverse fetal outcomes and transmission risk. However, concerns for ART association with preterm birth and low birth weight merit ongoing monitoring and discussion with the patient.⁵¹ In addition, new data suggesting a possible increased risk of neural tube defects among women in Botswana who took dolutegravir around the time of conception have raised concerns about the use of this medication in the first trimester.⁵² HIV-positive women of childbearing age who take dolutegravir and are not on effective contraception should be counseled regarding these findings and switched to alternative ART if appropriate.

Engagement in Care and the Fourth Trimester

Special efforts should be made to ensure engagement in HIV care for pregnant women, using medical case management resources and coordinating HIV and prenatal care visits when possible. A time of particular risk for HIV-positive pregnant women is the so-called fourth trimester postpartum period when engagement in care may flag because of postpartum depression, focus on the infant, and reduced intensity of efforts by medical providers.⁵³ A recent study in the United States examined retention in HIV care postpartum and found that receiving less than 12 weeks of antenatal ART was negatively associated with HIV care retention at 24 months postpartum, underscoring the importance of efforts to maximize engagement in care throughout the peripartum period.⁵⁴ Maintaining adherence to ART is important for all women, but of particular concern in this scenario are women who may experience repeat pregnancies during this time period.

Human Immunodeficiency Virus Controllers

Case 4: a 62-year-old woman presented to establish care after moving from another part of the country. She was referred for her current visit after a hospitalization for abdominal aortic aneurysm repair, at which time she reported a history of HIV. Her past medical history also includes hypertension, mild renal insufficiency, and a history of treated latent tuberculosis infection. She was diagnosed with HIV in 1994 and has never been on ART. She had been told that she has a low viral load and high CD4 count and did not require ART, and has not received care for her HIV in several years. Review of available records reveals that 4 years after HIV diagnosis her CD4 count was 590 cells/mm³ (45%) and her HIV viral load was less than 400 copies/μL, the lower limit of detection of the assay. Additional CD4 counts over an 8-year period ranged from 500 to 900 cells/mm³, with HIV viral load measurements less than the level of detection of the assay and most recently less than 50 copies/μL. She is reluctant to initiate ART based on her discussions with her prior HIV medical providers.

A small proportion (<1%) of people with HIV have low or undetectable levels of viral replication and maintain high CD4 counts. This group is referred to as HIV controllers, with those who never have detectable HIV viremia further categorized as elite controllers. Among elite controllers, some HIV replication occurs (although less than the typical limits of detection) and this population shows sequelae of inflammation and immune activation more commonly associated with HIV in their noncontroller counterparts.⁵⁵ An examination of coronary atherosclerosis among a group of elite controllers not on ART compared with PWH on ART and HIV-negative controls revealed that rates of coronary artery disease among the elite controllers were comparable with those of the noncontrollers on ART, and some inflammatory markers were higher.⁵⁶

Further, an analysis of non-AIDS-related events and all-cause hospitalizations among elite controllers and other HIV-positive persons on ART showed a 3-fold higher rate of cardiovascular hospitalizations among elite controllers compared with their treated counterparts.⁵⁷ Additional studies have shown that ART is of benefit in reducing markers of inflammation and immune activation among elite controllers, likely because of further reduction in viral replication.^{58,59} It is concerning that these studies have also shown less CD4 recovery than expected in elite controllers with ART initiation, reflecting possible harm in deferring ART.^{60,61}

For this patient, a careful discussion of these data is warranted. Conceptually, initiating a medication without measurable benefit on standard laboratory monitoring (eg, HIV RNA) may be a difficult case to make, particularly given the counseling she received in the past. Given her evolving clinical status with regard to her vascular disease (including her chronic renal insufficiency), the authors recommend focusing on ART as a component of health optimization and a logical measure in an effort to avoid further vascular inflammation. For PWH with less dramatic and demonstrable vascular disease or other comorbidities, the opportunity to prevent so-called silent vascular damage, malignancy, and other sequelae of inflammation and immune activation should be discussed. If ART is not initiated, regular engagement in HIV care is recommended to monitor for viremia and to assess readiness to initiate ART.

WHEN SHOULD ANTIRETROVIRAL THERAPY BE DELAYED?

Case 5: a 40-year-old man was brought to the emergency department by his family because of confusion. He reported mild headaches and weight loss over the prior 2 weeks, and had an abrupt onset of severe headache and confusion 1 day before presentation. In the emergency department, he became agitated and was unable to speak. A computed tomography scan of the head showed no mass lesions or other gross abnormalities. Lumbar puncture was performed with opening pressure increased at 30 cm H₂O. Cerebrospinal fluid (CSF) examination showed 25 nucleated cells with 88% lymphocytes, protein 151 mg/dL, and glucose of 36 mg/dL. Cryptococcal antigen level in CSF was increased to 1:10,000. A Gram stain of the CSF revealed 2+ yeast, and culture grew *Cryptococcus neoformans*. HIV Ag/Ab testing was reactive. CD4 count was 27 cells/mm³ (5%) and HIV RNA was 645,300 copies/μL.

In patients with AIDS and most opportunistic infections (OIs), major guidelines have recommended initiation or reinitiation of ART within the first 2 weeks after diagnosis of OI.^{3,62} In the setting of AIDS-related malignancy, immediate ART initiation is supported.⁶³ However, 2 specific clinical entities warrant consideration of a delay in ART initiation after initiation of OI therapy because of concern for paradoxical clinical worsening secondary to immune reconstitution inflammatory syndrome (IRIS): cryptococcal meningoen­cephalitis and active tuberculosis (particularly tuberculosis involving the central nervous system) (Box 4).

Cryptococcal Meningoencephalitis

Cryptococcal meningoen­cephalitis is a hallmark of advanced AIDS and is often fatal within weeks of presentations such as this patient's. It is more common at CD4 counts less than 100 cells/mm³ and most common at CD4 counts less than 50 cells/mm³, representing severely delayed diagnosis or difficulty accessing HIV care and ART. Although assessment for increased intracranial pressure (ICP) and initiation of induction therapy is a priority, planning should begin immediately for linkage to HIV care and access to ART once the patient is clinically ready, as well as medical case management if available. Once treatment is underway, virologic suppression is critical to allow a chance for recovery and to avoid relapse.

The concern for starting ART sooner than 2 weeks after completion of induction therapy for this patient is the risk of ICP secondary to IRIS while significant fungal burden remains. Debate persists regarding the safest time to initiate ART in presentations like this patient's, particularly with low CSF lymphocyte count and increased ICP.^{3,62,64,65} In high-resourced settings, when close monitoring is possible and the clinical setting allows easy access to monitoring of ICP, a more nuanced decision regarding timing of ART is possible, with acceptable intervals ranging from 2 weeks after completion of antifungal induction therapy until completion of the induction/consolidation phase (10 weeks). This approach requires treatment or prevention of concomitant OIs and hinges on a commitment to initiate ART at the earliest safe interval.

Trials evaluating early ART (within 2 weeks of diagnosis) in sub-Saharan Africa found significantly higher mortality with early ART, particularly within 2 to 5 weeks after diagnosis.⁶⁶ High rates of unmasking subclinical cryptococcal meningitis after ART initiation also remain a concern in these settings.⁶⁷ A review of pooled data suggests higher mortality risk associated with ART initiation within 4 weeks of diagnosis of cryptococcal meningoen­cephalitis in low-income and middle-income countries, although it is unclear whether this higher risk can be attributed to IRIS.⁶⁸

Tuberculosis

For PWH with pulmonary tuberculosis and CD4 counts less than 50 cells/mm³, results of a randomized clinical trial support starting ART within 2 weeks after initiation of antituberculosis therapy.⁶⁹ Although IRIS was more common with earlier versus later ART, PWH with low CD4 counts who started early ART had significantly lower rates of new AIDS-defining illnesses and death. This effect was not seen in PWH who started early ART

with CD4 counts greater than or equal to 50 cells/mm³, for whom ART within 8 weeks of initiating treatment of tuberculosis is recommended. For PWH and tuberculosis involving the central nervous system, a delay in ART initiation is recommended for at least 8 weeks following start of antituberculosis treatment.^{3,69,70}

Certain human immunodeficiency virus controllers—Case 4 is an example of an HIV controller who was found to have intermittent low-level viremia and concomitant vascular disease who initiated ART. In the absence of detectable viremia or relevant comorbidities, the benefit of ART is less clear. PWH who are HIV controllers and have maintained an undetectable HIV viral load for years may be observed off ART. Routine viral load monitoring is warranted.⁵

SUMMARY

The concordance of major guidelines groups regarding the benefit of ART at all stages of HIV infection and the advent of effective, well-tolerated, and durable ART have made the decision to initiate therapy easier for many providers and PWH. However, the importance of comprehensive support measures to ensure access to the projected long-term benefits of ART for all PWH, particularly low-income persons and the working poor, cannot be understated and is consistently under threat of funding shortfalls. Despite viral suppression, disparities in health outcomes for many men and women with HIV underscore the need for uninterrupted, frictionless access to health care. Further evaluation is needed to determine the most cost-effective and well-tolerated regimens, including generics, in a time of increased scrutiny of health care costs. Most importantly, HIV stigma continues to be the most persistent barrier to universal ART, the most common indirect cause of death from AIDS, and the obstacle to the deserved benefits of longevity and improved quality of life for all persons with HIV.

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Box 1**Initiation of antiretroviral therapy during acute human immunodeficiency virus infection**

- May allow greater recovery of CD4+ T-lymphocyte count and function
- Reduction in the latent viral reservoir
- Attenuates but does not fully resolve the chronic inflammation associated with all-cause morbidity and mortality risk in treated HIV infection
- Prevents HIV transmission

Box 2**Rapid antiretroviral therapy initiation**

- Reduces time to viral suppression and confers associated immunologic benefits
- May improve retention in HIV care
- Requires coordinated multidisciplinary services and a commitment to streamline access to ART

Box 3**Challenges to implementing rapid antiretroviral therapy**

- PWH may not be ready to initiate ART on the day of diagnosis.
 - Risks and benefits of immediate ART should be offered; rapid ART initiation should be presented as standard of care to maximize therapeutic benefit.
- Securing access to same-day ART supply and a reliable mechanism for ongoing ART supply is challenging.
 - There are numerous bureaucratic barriers to immediate access to ART regardless of payor source; burdensome eligibility requirements for patient assistance programs create further delay.
 - Coordinating rapid ART start is resource intensive and may not be feasible without multidisciplinary collaboration by care teams.
- Health care providers are faced with competing demands during the initial visit.
 - HIV counseling, addressing comorbid psychiatric and medical conditions, addressing substance abuse, food and housing insecurity, and helping PWH navigate insurance and pharmaceutical assistance programs can shift focus from ART initiation.
 - Clear delineation of roles within a multidisciplinary care team may help providers focus on medical issues and ART start.
- Health care providers may be reluctant to start ART without complete laboratory data.
 - Several first-line regimens are appropriate for initiation in the absence of baseline genotypic data. Similarly, prior regimens and laboratory data may be used to guide choice of ART in patients reentering care. The Rapid Entry and ART in Clinic for HIV (REACH) program in Atlanta successfully implemented an ART rapid start program and used provider education to streamline this process.³³
- Rapid ART start confers additional risk for adverse effects of therapy, particularly among patients with advanced HIV.
 - PWH considered for rapid start of ART should be screened for signs and symptoms of opportunistic infections, particularly cryptococcal meningitis or tuberculosis, to avoid immune reconstitution inflammatory syndrome.
- Early ART initiation raises concern for development of drug resistance.

- The HIV-CAUSAL collaboration, a large multisite cohort, found a low risk of acquired drug resistance with longer durations of ART, supporting the safety of early initiation of ART.³⁵

Box 4**When to delay antiretroviral therapy**

- Cryptococcal meningoencephalitis
- Tuberculosis
- Certain HIV controllers

KEY POINTS

- Antiretroviral therapy (ART) is recommended for all individuals with human immunodeficiency virus (HIV), regardless of CD4 count, to reduce the morbidity and mortality associated with HIV infection and to prevent transmission of HIV.
- The evidence for immediate and universal ART is strong, clearly showing individual and population-level benefits, and is supported by all major guidelines groups.
- ART should be initiated as soon as possible after HIV diagnosis, including at the time of diagnosis if feasible and acceptable to the patient.
- ART should be continued without interruption to maintain virologic suppression.
- Delayed ART may be warranted in the setting of active tuberculosis or cryptococcal meningitis; the benefits of treatment of HIV controllers is also unknown.

Fig. 1.

Summary of major advances and clinical trials supporting universal ART for HIV infection regardless of CD4 count. (A) Improvements in ART. The advent of HAART in 1995 led to significant improvements in ART efficacy but initially carried substantial side effects limiting tolerability of regimens. Single-tablet regimens and integrase strand inhibitors changed the landscape of ART after 2006. Modern ART regimens are more potent, durable, and efficacious, with substantially improved tolerability. (B) Clinical benefits. Summary of the 3 randomized clinical trials showing significant reductions in mortality or serious adverse events when ART is initiated at higher CD4 cell counts. (C) Decreased transmission. Three trials showed substantial reduction in HIV transmission among serodiscordant couples, including men who have sex with men. ^a In HPTN 052, no phylogenetically linked

infections were observed when HIV-1 infection was stably suppressed in the HIV-positive partner.³⁶ INSTI, integrase strand transfer inhibitor.

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Table 1

Guideline recommendations: when to start antiretroviral therapy

Current Guidelines	Recommendation
International Antiviral Society -USA Panel 2018 ³	ART is recommended for virtually all individuals infected with HIV, as soon as possible after diagnosis
World Health Organization 2017 ⁴	Rapid ART initiation should be offered to all people with HIV following a confirmed HIV diagnosis and clinical assessment
US Department of Health and Human Services 2018 ⁵	ART is recommended for all individuals with HIV, regardless of CD4 count, to reduce the morbidity and mortality associated with HIV infection
European AIDS Clinical Society 2018 ⁶	ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts. Rapid start at time of HIV diagnosis is feasible, acceptable, and should be considered when possible

Table 2

Key practice-changing studies influencing recommendations for near-universal antiretroviral therapy

Year Findings Made Public	Study	Key Findings
2006	SMART ⁹	Deferred ART initiation until CD4<250 cells/mm ³ was associated with higher morbidity and mortality compared with initiation of ART at CD4 >350 cells/mm ³ . Continuous ART prevented both AIDS and non-AIDS events; episodic use of ART increased risk of opportunistic infection or death and did not prevent adverse effects associated with ART
2009	ART CC ¹⁰	Deferred ART initiation until CD4<350 cells/mm ³ was associated with higher mortality than initiation at higher CD4. Earlier ART initiation conferred increased life expectancy
2009	NA-ACCORD ¹¹	ART initiation in CD4 350–500 cells/mm ³ range decreased mortality vs deferred initiation; mortality reduced further with ART initiation at CD4 >500 cells/mm ³ vs deferred
2010	CIPRA HT 001 ¹²	ART initiation at CD4>350 cells/mm ³ decreased rates of death and incident tuberculosis compared with deferred initiation at CD4<200 cells/mm ³ among participants in Haiti
2011	HPTN 052 ¹³	Treatment as prevention: HIV transmission was essentially eliminated in serodiscordant couples when the HIV-positive partner was on ART; morbidity and mortality benefits were seen for partners on ART
2015	TEMPRANO ⁷	Early ART (CD4>800 cells/mm ³) and isoniazid preventive therapy independently reduced the risk of severe morbidity among participants in Côte d'Ivoire
2015	START ⁸	Immediate ART reduces risk of AIDS and non-AIDS events regardless of CD4 count. Notably, study halted by independent Data and Safety Monitoring Board to recommend that participants in arm deferring ART until CD4 count reached 350 cells/mm ³ should receive ART