PROTOCOL FOR THE IMPLEMENTATION OF RAPID ANTIRETROVIRAL THERAPY INITIATION (RAPID ART)

Protocol developed by:
TIES project – Ending the HIV Epidemic in the U.S. (EHE)
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Acronyms and glossary for the Protocol for Rapid Antiretroviral Therapy Initiation (Rapid ART)

ADAP = AIDS Drug Assistance Programs

EMA = Eligible Metropolitan Area

RNA = Ribonucleic Acid

ARV = Antiretroviral

ATF = AIDS Task Force

BMP = Basic Metabolic Panel

BUN = Blood Urea Nitrogen

CAI = Cicatelli Associates, Inc.

CBC = Complete Blood Count

CCR5 = CC Chemokine Receptor 5

CD4 = T Lymphocytes or helper T cells

CDC = Centers for Disease Control and Prevention

CMP = Comprehensive Metabolic Panel

CrCl = Creatinine Clearance

VL = Viral load

DHHS = Department of Health & Human Services

EHE = Ending the HIV Epidemic in the U.S.

STD = Sexually Transmitted Diseases

US = United States

FDA = Food and Drug Administration

HAART = Highly Active Antiretroviral Therapy

HAB = HIV/AIDS Bureau

HBcAb = Hepatitis B core Antibody

HBsAb = Hepatitis B surface Antigen

HBsAg = Hepatitis B Surface Antigen

HIVTMD = HIV Treaters Medical Association of Puerto Rico

HLA-B * 5701 = Screening test to measure the risk of hypersensitivity reaction to Abacavir.

HRSA = Heath Resources and Services Administration

U = U = Undetectable = Untransmittable

FI = Fusion Inhibitor

INSTI = Integrase Strand Transfer Inhibitors

OI = Opportunistic Infection

PI = Protease Inhibitor

Rapid ART = Rapid Antiretroviral Therapy

NRTIs = Nucleoside Reverse Transcriptase Inhibitors

NNRTIs = Non-Nucleoside Reverse Transcriptase Inhibitors

STI = Sexually Transmitted Infection

LFT = Liver Function Test

mg = Milligrams

ml/min = Milliliter / Minute

mm^3 = Cubic Millimeter

MTCT = Mother-to-Child Transmission

NNLM = Network of the National Library of Medicine

NTD = Neural Tube Defects

NtRTI = Reverse Transcriptase Nucleotides

NYSDOH = New York State Department of Health

WHO = World Health Organization

PEP = Post-exposure Prophylaxis

PrEP = Pre-exposure Prophylaxis

TIES Project

RAM = Resistance Associated Mutations

AIDS = Acquired Immunodeficiency Syndrome

IRIS= Immune Reconstitution Inflammatory Syndrome

TAP-in = Technical Assistance Provider – innovation network

ART = Antiretroviral Therapy

TasP = Treatment as Prevention

TB = Tuberculosis

UA = Urinalysis

VDRL = Screening test for Syphilis

HAV = Hepatitis A Virus

HBV = Hepatitis B Virus

HCV = Hepatitis C Virus

HIV = Human Immunodeficiency Virus

Classification of HIV infection among adolescents and adults:

Categories according to CD4 lymphocytes	**Clinical categories**
	A = Asymptomatic, Persistent Generalized Lymphadenopathy (PGL) or acute HIV infection
1) >500cells/mm^3 (>29%)	A1
2) 200 – 499 cells/mm^3 (14 – 28%)	A2
3) <200cells/mm^3 (<14%)	A3 Condition reported as AIDS

1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. MMWR DEC 18, 1992/41 (RR-17)

Drugs:

1. **TAF/FTC/BIC** = Tenofovir alafenamide/ emtricitabine/bictegravir = Brand Name: **Biktarvy**
2. **TAF/FTC** = Tenofovir alafenamide/emtricitabine = Brand Name: **Descovy**
3. **DTG** = Dolutegravir = Brand Name: **Tivicay**
4. **TAF/FTC/DRV/COBI** = Tenofovir alafenamide/emtricitabine/darunavir/cobicistat = Brand Name: **Symtuza**
5. **ABC** = Abacavir = Brand Name: **Ziagen**
6. **RPV** = Rilpivirine = Brand Name: **Edurant**
7. **EFV** = Efavirenz = Brand Name: **Sustiva**
8. **TDF/FTC** = Tenofovir disoproxil fumarate/emtricitabine = Brand Name: **Truvada**
9. **ATV** = Atazanavir = Brand Name: **Reyataz**
10. **RTV** = Ritonavir = Brand Name: **Norvir**
11. **DRV** = Darunavir = Brand Name: **Prezista**
12. **RAL** = Raltegravir = Brand Name: **Isentress**

Glossary:

1. **Treatment-Naive** = When an individual with HIV has never taken antiretroviral drugs.
2. **Program Income** = Program income generated and received as a result of receiving a grant award from RWHAP. They are most commonly generated by recipients and subrecipients as a result of charging for services and receiving reimbursement payments from third parties.
3. **340b Drug Pricing Program** = US federal program that requires drug manufacturers to provide outpatient medications to eligible entities at significantly reduced prices.
4. **Best Practices**
5. **Unboosted**

Introduction

Under the *Ending the HIV Epidemic in the U.S.* (EHE) initiative in San Juan, Puerto Rico, the Autonomous Municipality of San Juan, through the TIES Project ascribed to *AIDS Task Force* (ATF), has commissioned the development of a core protocol that serves as a guide in the implementation processes of the strategy of rapid antiretroviral therapy initiation in people with a reactive result in the rapid HIV detection test, with a new diagnosis of HIV, or people with a previous diagnosis of HIV outside of treatment.

This protocol was developed to encourage the initiation of antiretroviral therapy (ART) ideally on the same day of a preliminary positive HIV+ result or within 7 days of a positive preliminary result, with an approach called "Rapid ART Initiation" (Rapid ART). The initiation of ART on the same day in which an individual has a reactive result in the HIV detection test, or is diagnosed with HIV, or at the first clinic visit is a recommended standard of care for HIV treatment and it is promoted by the ATF. In order to support the standard of initiating ART after a preliminary positive result, this protocol:

- Provides guidance for choosing safe and effective ART regimens based on known patient characteristics before the results of recommended resistance tests or baseline laboratory tests are available.
- Identifies the antiretroviral regimens that should be avoided for the rapid initiation of ART.
- Provides guidance to recognize when rapid initiation is not appropriate.
- Encourages doctors to consult and seek the help of an experienced medical provider when managing patients with various comorbidities.
- Integrates current evidence-based clinical recommendations and healthcare-related implementation strategies from the *Ending the HIV Epidemic in the U.S. (EHE)* initiative, which seeks to end the HIV epidemic in the United States by 75% in the next 5 years and 90% in 10 years, by the end of 2030. The goal for 2030 is to reduce new HIV infections to less than 3,000 (90%) in the US and its territories.
- Provides guidance on funding sources for sustainable access to ART.

For the development of this protocol, several sources of information and protocols established in pioneering jurisdictions in rapid ART initiation were consulted, such as New York and San Francisco. The rapid initiation protocol described in this guide is an adaptation of the New York Department of Health protocol. The references and studies included in this protocol were obtained from: *When to Initiate Antiretroviral Therapy, With Protocol for Rapid Initiation* [Radix and Shalev, 2021], developed by the New York State Department of Health AIDS Institute and were included faithfully and accurately.

This guide and the protocol for rapid ART initiation was reviewed and validated by a group of experts in Puerto Rico, which includes the following professionals:

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BENEFITS AND RISKS OF ART

According to the US Food and Drug Administration (FDA), antiretroviral therapy (ART) refers to the use of pharmacological agents that have specific inhibitory effects on HIV replication. The use of less than three agents to initiate rapid treatment is not recommended. These agents belong to six different classes of drugs: nucleoside reverse transcriptase inhibitors and reverse transcriptase nucleotides (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PI), fusion inhibitors (FI), CCR5 co-receptor antagonists and integrase strand transfer inhibitors (INSTI). View all commercially available antiretroviral drugs that are approved by the FDA. For rapid ART initiation, refer to the tables of preferred and alternative regimens in the tables below.

Benefits of ART

Several randomized clinical trials have shown the benefits of ART in reducing HIV-related morbidity and mortality, regardless of the degree of immunosuppression at the initiation of treatment [Severe, et al. 2010; Lundgren, et al. 2015]. Therefore, ART should be recommended for all people with HIV infection.

With proper selection of an initial regimen and good patient adherence, durable virologic suppression (i.e., lifelong control of the viral load) is achieved in virtually all patients with HIV infection. Virologic suppression almost invariably leads to immune recovery, followed by reductions in the incidence of opportunistic infections and malignant neoplasms.

Measurable goals of the treatment include the following:

1. Viral suppression measured by the level of HIV-1 RNA below detection limits.
2. Immune reconstitution due to an increase or maintenance of the CD4 cell count.
3. Reduction of complications associated with HIV, including AIDS-related and non-AIDS-related conditions.

ART also reduces morbidity and mortality from non-HIV-related causes. In a randomized study that compared continuous ART with CD4-guided treatment interruption, a mortality benefit was seen in participants on continuous ART [El-Sadr, et al. 2006]. This benefit was attributed to a reduction in deaths from cardiovascular, renal, and hepatic causes. ART decreases the inflammatory environment associated with ongoing HIV replication. ART-mediated reductions in proinflammatory cytokines are assumed to lead to lower rates of clinical complications associated with the proinflammatory state [Hileman and Funderburg 2017].

Reduction of HIV transmission

In addition to its direct benefit to the health of the individual with HIV infection, ART is a critical component in eliminating HIV transmission. Antiretroviral treatment as prevention (TasP) is associated with greater reductions in HIV transmission than any preventive modality studied to date. In the *HIV Prevention Trials Network* (HPTN 052), a large randomized clinical study of serodiscordant couples, early treatment of the HIV-positive partner was associated with a 96% reduction in HIV transmission compared with a late treatment approach [Cohen, et al. 2011]. One third (36%) of the infections identified in couples who entered the study were acquired from another partner. In the long-term follow-up of study participants, linked transmissions between couples were thought to occur only when the index partner was vireamic [Cohen, et al. 2016]. In the PARTNERS observational study, no phylogenetically linked HIV transmission was observed in serodiscordant couples in which the partner with the positive diagnosis had a detectable viral load and was virologically suppressed with ART [Rodger, et al. 2016]. In the PARTNERS2 study, the findings indicated that there was no HIV-related transmission during approximately 77,000 acts of anal sex without condom, during anal sex without condom among serodifferent gay men when the HIV-positive man had a viral load of <200 copies/mL. The findings of these studies support the message of the U=U (undetectable equals untransmittable) campaign and the benefits of early HIV testing and treatment [Roger. et al. 2019].

Therefore, the evidence suggests that the risk of sexual transmission of HIV during virologic suppression is insignificant. ART should be recommended for all patients with HIV infection to prevent transmission to sexual partners and, by extrapolation, to partners who share needles. Despite its powerful benefit in reducing HIV transmission, ART is not a substitute for the use of condoms or clean syringes. These harm reduction measures, along with the use of Pre-Exposure

Prophylaxis (PrEP) for partners who do not have HIV infection, will help reduce the incidence of other STIs and viral hepatitis, and should be integrated into patient counseling at the initiation of ART.

Reduction of complications

Accumulating evidence suggests that patients who initiate ART earlier or spend less cumulative time with detectable plasma viremia are less likely to experience certain complications, such as cardiovascular disease [El-Sadr, et al. 2006; Marin, et al. 2009; Ho, et al. 2010; Lichtenstein, et al. 2010; Ho, et al. 2012], neurocognitive dysfunction [Tozzi, et al. 2007; Ellis, et al. 2011; Garvey, et al. 2011; Winston, et al. 2012], decreased risk of serious bacterial infections [O'Connor, et al. 2017], and some non-HIV-related malignant neoplasms [Bruyand, et al. 2009; Guiguet, et al. 2009; Silverberg, et al. 2011; Sigel, et al. 2012]. The data also demonstrate that although older patients are likely to achieve virologic suppression, they are less likely to achieve an immunologic response, as measured by a CD4 count increase of 100 cells/mm3, and that patients of >55 years of age may be at increased clinical risk even after initiation of therapy [Sabin, et al. 2008]. The poor immune recovery seen in older patients is associated with increased morbidity and mortality, cardiovascular events in particular [van Lelyveld, et al. 2012]. In one study, men aged ≥50 who initiated ART with CD4 counts in the range of 351 to 500 cells/mm3 were able to achieve immune responses similar to those of younger men who initiated with lower CD4 counts [Li X, et al. 2011].

Reduction of mother-to-child transmission of HIV and among serodiscordant heterosexual couples

Studies have shown that for HIV-positive pregnant women, the administration of ART during pregnancy or intrapartum significantly reduces the risk of mother-to-child transmission (MTCT) of HIV [Connor, et al. 1994; Guay, et al. 1999]. A large study showed a 96% reduction in the transmission among serodiscordant heterosexual couples when the positive partner was receiving ART [Cohen, et al. 2011], adding to the body of evidence that lower viral load reduces the risk of transmission.

ART is now part of the established strategy to reduce HIV transmission and is an essential component of prevention interventions alongside counseling for risk reduction, safer sexual practices and avoiding needle sharing. Although most patients worldwide are identified late in the

course of their HIV infection [Althoff, et al. 2010; CDC 2010, 2011], efforts to routinely offer universal HIV testing to all patients over the age of 13 is a very effective strategy in the early detection of people living with HIV so that they can benefit from immediate treatment.

RISKS OF ART

Despite the excellent tolerability of contemporary ART regimens, the adverse reactions, side effects, long-term drug toxicities, and drug interactions continue to pose some limited or relative risks. Patients should be counseled about the potential for short- and long-term ART-associated adverse events. These risks include tolerability issues which may affect quality of life, as well as potential long-term toxicities, primarily a low relative risk of renal and cardiovascular disorders or decreased bone density of uncertain clinical significance [Friis-Moller, et al . 2010; Monteiro, et al. 2014; Hoy, et al. 2017]. Renal and bone density issues are largely eliminated with newer antiretroviral (ARV) formulations. Fatal reactions from ART drugs are extremely rare.

Many ART combinations are now available in single-pill, fixed-dose combined formulations. Thus, the amount of pills associated with early antiretroviral regimens has been largely eliminated. However, lifelong medication adherence can be challenging for some individuals, particularly when treatment with a single daily tablet is not feasible.

Compared with earlier antiretroviral combinations, contemporary ART regimens are associated with higher rates of durable virologic suppression. The lack of virologic suppression in a patient on ART should prompt the doctor to assess patient adherence and provide intensive support for those individuals who report challenges in this area. Failure to achieve and maintain virologic suppression can lead to the emergence of resistance-associated mutations (RAMs). One study has shown that virologic failure with contemporary ART regimens is associated with the infrequent occurrence of RAMs [Scherrer, et al. 2016]. However, RAMs can arise with current first-line therapies. Antiretroviral drugs resistance may compromise the potential for long-term virologic suppression, simple dosing schedules, and the tolerability of future treatment options.

The initiation of ART is associated with a risk of immune reconstitution inflammatory syndrome (IRIS). IRIS is a clinical syndrome characterized by new or worsening infectious and non-infectious complications observed after the initiation of ART. The risk of IRIS is increased when ART is initiated with low CD4 cell counts (<100 cells/mm3) or with the presence of specific

opportunistic infections. Although the risk of IRIS is not a contraindication for the initiation of ART, doctors and patients should be aware that the risk of developing IRIS is increased among people with lower CD4 counts. Higher-risk patients should be informed of the possibility of paradoxical clinical worsening after the initiation of ART. Patients with cryptococcal or tuberculous meningitis should not be initiated on antiretroviral treatment if they have not already been initiated on specific treatment for these infections to avoid the risk associated with IRIS in these opportunistic infections.

Risks of untreated HIV

The results of the START study [Lundgren, et al. 2015] and data show that untreated HIV infection leads to increased morbidity and mortality from HIV-related and non-HIV-related conditions, even with high CD4 counts. Together with the dramatic reduction of the risk of transmission with an effective treatment, these data support the initiation of ART regardless of the CD4 count in all adequately treated patients, including patients diagnosed with acute HIV infection. Treated patients who are documented long-term nonprogressors or elite controllers are a group that may deserve special consideration.

In START, a randomized trial that initiated ART in patients without prior treatment with CD4 counts of >500 cells/mm3 versus expecting a decline to ≤350 cells/mm3 before initiation, demonstrated a 53% reduction in severe disease and death in the early ART group [Lundgren, et al. 2015]. Data from NA-ACCORD, an observational study, demonstrated that both morbidity and mortality improved upon initiation of ART in patients with CD4 counts in the high or even normal range [Kitahata, et al. 2009]. A significantly decreased risk of death was observed in patients who initiated treatment with CD4 counts of >500 cells/mm3 compared with those who deferred to <500 cells/mm3, as well as in those who initiated ART in the range of 350 to 500 cells/mm3 compared to those that deferred to <350 cells/mm3 [Kitahata, et al. 2009]. Although other studies have demonstrated only a minimal survival advantage [Wright, et al. 2011] or no survival advantage among those who initiated ART at the highest CD4 counts, they did confirm the benefits of initiating ART at levels of ≤500 cells /mm3 [Cain, et al. 2011; CASCADE 2011 collaboration; Young, et al. 2012]. Another study demonstrated an approximately 33% reduction in the risk of death from end-stage liver disease, non-AIDS-related infections, and non-AIDS-defining cancers with each 100 cell/mm3 increase in CD4 count [Marin, et al. 2009]. A randomized study of early

versus deferred therapy in patients with CD4 counts in the range of 350-550 cells/mm3 showed no mortality benefit [Cohen, et al. 2011]; however, this study has significant limitations, especially a relatively short follow-up period.

JUSTIFICATION FOR RAPID ART INITIATION

Reduction of treatment delays and loss to follow-up

Standard practice protocols for ART initiation have produced preventable delays. The wait required for confirmatory HIV diagnosis and the results of baseline laboratory tests including resistance tests, together with the required medical visits, may unnecessarily delay the initiation of treatment by up to 4 weeks. Problems accessing health insurance or waiting for public benefits to activate can also cause delays. It is estimated that, in 2016, only 75.9% of individuals diagnosed with HIV on the HIV care continuum in the United States were linked to care within 1 month [CDC 2018]. People living with HIV who are not linked to medical care are at risk of sustained viral loads and continued transmission of HIV.

Benefits for HIV patients

Several observational and clinical trials have demonstrated the individual-level benefits of rapid ART initiation [Ford, et al. 2018]. A pilot study of this approach in San Francisco, California, showed that patients who initiated ART within 1 or 2 days had a shorter time (median, 1.8 months) to achieve viral suppression (HIV RNA ≤200 copies/ ml) than those offered standard of care (4.3 months) or historical controls (7.2 months) [Pilcher, et al. 2017]. Longer-term follow-up of 225 patients at the same center found that of the patients who had access to rapid initiation, 95.8% had achieved viral suppression at least once and 92.1% had achieved it at the last visit registered [Coffey, et al. 2019]. These individual-level benefits have been replicated in other US and international studies that demonstrated better viral suppression with shorter time to ART initiation [Rosen, et al. 2016a; Koenig, et al. 2017; Colasanti, et al. 2018]. After implementing rapid ART initiation in a hospital clinic in Atlanta, Georgia, the time to viral suppression fell from 77 days, prior to intervention, to 57 days [Lundgren, et al. 2015], and the average time to ART initiation decreased from 21 to 7 days; both findings were statistically significant [Colasanti, et al. 2018].

Another demonstrated benefit is a better rate of retention in care [Amanyire, et al. 2016; Rosen, et al. 2016a; Koenig, et al. 2017]. In the RapIT trial in South Africa, newly diagnosed HIV patients were randomized to rapid ART initiation or standard care [Rosen, et al. 2016b]. Participants in the rapid initiation group had higher rates of ART initiation at 90 days (97% vs. 72%) and higher rates of retention in care and viral suppression (HIV RNA ≤400 copies/mL) at 10 months (relative risk, 1.26 [1.05–1.50]). The average cost per patient to achieve viral suppression was lower among those on rapid ART initiation, demonstrating that this strategy may also be cost-effective [Long, et al. 2017]. Studies from China and South Africa support the cost effectiveness of rapid ART initiation [Zulliger, et al. 2014; Wu, et al. 2015; Ford, et al.2018]. Rapid ART initiation is effective, safe, and highly acceptable, with few patients refusing the offer of immediate ART [Pilcher, et al. 2017; Coffey, et al. 2019].

Rapid ART initiation is safe

In the San Francisco study discussed above [Pilcher, et al. 2017], 89.7% of patients used regimens that contained integrase strand transfer inhibitors (INSTI), and 12.8% used regimens that contained protease inhibitors. The predominant INSTI-based regimen was dolutegravir plus emtricitabine/tenofovir disoproxil fumarate. The clinic had no cases of major resistance mutations to the prescribed ART regimen, and no regimen changes were made due to resistance. Two patients had their regimen changed due to skin rash, and in 10 cases the regimen was simplified to a single-tablet regimen.

Out of 149 patients who initiated ART through a program in New York City, only 1 patient required a regimen change due to later-detected resistance [Blank, et al. 2018].

Rapid ART initiation is safe. Most of the regimens designated for rapid ART initiation are the same regimens that are recommended as initial treatment by the Federal Department of Health. These regimens are well tolerated and effective, and the likelihood of drug resistance is low based on the current prevalence of drug resistance [NYCDHMH 2018]. A recent study used a combined drug of two therapies (dolutegravir and lamivudine) for rapid treatment. The vast majority of patients achieved sustained virologic suppression (97% observed, 82% ITT, 76% FDA), and no emerging mutations were observed in patients who had confirmed virologic failure [Paige, et al. 2021].

PROTOCOL

Rapid ART initiation

Rapid ART initiation can reduce delays and improve the rates of viral suppression among people living with HIV. Rapid ART initiation preferably on the same day or within 7 days of a recent positive HIV test is the strategy endorsed by the World Health Organization [WHO 2017] and is an essential component of the *Ending the HIV Epidemic in the U.S.* (EHE) initiative. Mathematical models demonstrate that a test-and-treat strategy together with immediate ART initiation and prevention approaches may lead to the elimination of new HIV infections [Granich, et al. 2009].

Identification of candidates for rapid ART initiation

In order to determine if a patient is a candidate for rapid initiation of ART, clinical staff must confirm that the individual:

- Has a reactive result in the rapid HIV detection test as the point of entry to care, or a confirmed diagnosis of HIV, or a suspected acute HIV infection, or a known HIV infection.
- Has not previously received ART treatment (naive) or had limited use of ART drugs.
- Has no medical conditions or opportunistic infections that require postponement of rapid ART initiation, including suspected cryptococcal or tuberculous meningitis.
- Participants with previous diagnosis, experienced and without medical evaluation for more than six months.

For patients with a reactive HIV antibody test pending confirmation, the doctor should ensure that they understand the benefits of rapid ART initiation and that:

- a reactive HIV antibody test result does not constitute a formal diagnosis since false-positive results exist;
- they will have a confirmatory (diagnostic) test for HIV;
- ART will be discontinued if the confirmatory test result is negative and continued if the result is positive;
- the benefit of initiating ART early, after a preliminary positive detection test, outweighs the risk of taking ART for a few days and then discontinuing it if confirmed negative by the confirmatory test.

The result of the confirmatory HIV test should be reported and given to the patient as soon as it is available. If the result is negative, discontinue ART and refer to preventive services including PrEP. If the result is positive for HIV, reinforce adherence and the next steps to follow.

If the patient refuses rapid ART initiation, discuss options for delaying treatment, link the patient to primary HIV care, and outline next steps. If the patient agrees to start with Rapid ART, a virtual communication plan (telemedicine) by phone or in person will be established within the first day to the third day to offer support in the decisions made. And a face-to-face appointment will be coordinated in the next 7-14 business days for follow-up or the necessary readjustment. This

communication plan will be offered considering and respecting all the protocols of confidentiality, privacy and informed consent.

Counseling and education

A reactive result in the HIV detection test should prompt a provider to counsel the patient about the benefits and risks of ART and about the risk of HIV transmission, including the consensus that undetectable equals untransmittable (U = U). When patients are initiated on ART on the same day as their reactive HIV test result, priorities for patient education and counseling should include:

- Confirming the HIV diagnosis.
- Managing diagnosis disclosure, if so indicated.
- Adhering to ART regimen.
- Recognizing and responding to medication side effects, interactions with other therapies, schedules, diet, and alternative therapies.
- Following-up with clinic visits.
- Evaluating health literacy.
- Management of lifelong ART: Navigating acquisition and payment for medications needed for lifelong therapy, including pharmacy selection, insurance requirements and restrictions, copayments, and prescription refills.
- Identifying and addressing psychosocial problems that may pose barriers to treatment including and identifying social determinants of health such as the need for transportation, child or dependent care, unemployment, cognitive or functional diversity, etc.
- Referrals for the management of problematic substance use and mental health counseling, if required.
- Referrals for housing assistance, if required.
- Ensuring that the patient knows how to contact the clinical team if necessary, to address medication adverse effects or other concerns.
- Health education on issues of sexuality, prevention and/or management of other sexually transmitted infections and HIV prevention strategies such as PrEP and Undetectable = Untransmittable.

According to the National Network of Libraries of Medicine, health literacy requires:

- The ability to understand prescription drug instructions, appointment scheduling, medical education brochures, physician instructions, and consent forms.
- The ability to negotiate with complex health systems.
- Reading, listening, analysis and decision-making skills, and the ability to put these skills into practice in health situations.

Medical and psychosocial assessment

The medical evaluation of a patient with a new reactive HIV test result should include history, signs, or symptoms of infection or opportunistic infections. ART should be delayed and appropriate medical treatment initiated if tuberculous (TB) or cryptococcal meningitis (see below) is suspected [WHO 2017], if cytomegalovirus retinitis is suspected, or if the patient has any evidence of advanced HIV disease in the clinical examination.

To identify the potential for preexisting drug-resistant viruses, the initial evaluation should also include the patient's history of pre-exposure prophylaxis (PrEP), use of post-exposure prophylaxis (PEP), and prior use of ART for people re-engaging in care [Ford, et al. 2018].

When taking a medical history before rapid ART initiation, ask about:

- Date, types of tests and result of the last HIV test.
- Status or serological status of sexual partners and their ART regimens, if known.
- Previous use of antiretroviral drugs, including the use of PrEP, PEP or limited use in pregnancy with the dates when they were used.
- Comorbidities, including a history of renal or hepatic disease, particularly hepatitis B infection.
- Prescription and non-prescription drugs and natural remedies or alternative therapies.
- Medication allergies.
- Illicit substance use or problematic substance use.
- Symptoms to evaluate active cryptococcal and tuberculous meningitis.

- Psychiatric history, particularly depressive or psychotic symptoms or any history of suicide.
- Assess history of trauma or abuse.
- Possible pregnancy and maternity plans in individuals of reproductive or potentially fertile age

Baseline laboratory and resistance tests

All patients with a reactive HIV test result should undergo the laboratory, baseline, or resistance tests described below:

- HIV-1/2 Antigen/Antibody Test
- Quantitative HIV viral load
- HIV-1 genotype (including NRTI, INSTI, PI)
- CD4+ T lymphocytes count
- HBsAg, HBcAb, HBsAb
- Antibody against Hepatitis C Virus (HCV)
- Metabolic panel (including creatinine and renal function tests (LFTs))
- IGG Antibody against Hepatitis A Virus (HAV)
- Urinalysis (UA)
- Screening Tests for Sexually Transmitted Infections (STIs): Serology of Syphilis (VDRL), Chlamydia and Gonorrhea. The tests could be in urine, rectal or pharyngeal as appropriate
- Pregnancy test for all individuals of reproductive capacity

IMPORTANT: The doctor can initiate the patient on ART while waiting for the results.

General principles in choosing a regimen for rapid ART initiation

- Doctors should involve their patients when deciding which antiretroviral therapy (ART) regimen is most likely to result in adherence.
- Before initiating ART, doctors should:
    - Assess the patient's prior use of antiretroviral medications, including pre-exposure prophylaxis (PrEP) and (PEP), which may increase the risk of background resistance.
    - Assess if there are comorbidities and use of other medications that may affect the choice of regimen to initiate ART.
    - At the time of HIV diagnosis, obtain genotypic resistance tests for the protease, reverse transcriptase, and integrase genes.
    - Ask individuals of reproductive age about the possibility of pregnancy, their reproductive plans, and their use of contraception.
- For patients without treatment, following antiretroviral therapy, doctors should select an initial ART regimen from the *Preferred and Alternative Regimens for rapid initiation of ART* listed in the tables below.
- Doctors should regularly assess and reinforce medication adherence.
- Doctors should obtain a viral load test 4 weeks after the initiation of ART to assess response to therapy.
- Doctors or a trained clinical team member should follow up within 24-48 hours (consider 48-72 hours), by phone, face-to-face, telemedicine, or other preferred method with a patient who has initiated ART to assess tolerance and adherence to medication.
- If possible, schedule an in-person visit 7-14 days after the initiation of ART. This visit could be carried out by the medical service provider, clinical staff, such as nursing staff, health promoter, clinical case manager or any other health professional with the tools and training in Rapid ART.

Choosing a regimen for rapid initiation of ART

The preferred drugs for rapid initiation of ART are based on established regimens for naive individuals and are restricted to those that can be initiated safely in the absence of readily available baseline laboratory test results, such as viral load, CD4 count and HLA-B*5701. Preferred regimens have a high barrier to resistance, are well tolerated, and limit the potential for drug interactions. Initial regimens should be selected on the basis of patient preferences and clinical characteristics, and a preferred regimen should be used whenever possible.
The 2-drug ART regimen of (dolutegravir/lamivudine [DTG/3TC]), brand name Dovato) is not recommended for rapid ART unless there is a test of resistance and hepatitis B at the time of rapid initiation, because a baseline profile of genotypic HIV resistance and hepatitis B virus status is required prior to prescribing this regimen.

An alternative regimen (tenofovir alafenamide/emtricitabine/darunavir/cobicistat [TAF/FTC/DRV/COBI, brand name Symtuza]) has been formally studied in the context of rapid ART initiation in a phase 3 prospective multicenter study without the benefit of resistance testing, and produced high rates (96%) of viral suppression (HIV RNA level of <50 copies/mL) at 48 weeks [Huhn, et al. 2019].

When following a rapid ART initiation protocol, healthcare providers should avoid the regimens containing abacavir (Brand Name Ziagen) since HLA-B*5701 test results are likely to be unavailable. Likewise, rilpivirine (Brand Name Edurant) should be avoided in patients with a viral load >100,000 copies/ml and in patients whose viral load is unknown.

Efavirenz (Brand Name Sustiva) is associated with a higher risk of side effects in the central nervous system and transmitted drug resistance mutations [Kagan, et al. 2019]; therefore, it is not recommended for rapid ART initiation.

Clinics that have implemented rapid ART initiation design pre-approved regimens that take into account local patterns of transmitted drug resistance and drug toxicity [Pilcher, et al. 2017].

There is a greater possibility that HIV drug resistance mutations emerge and reduce the efficacy of an initial ART regimen in patients with a new reactive screening HIV test or a new HIV diagnosis who have taken tenofovir disoproxil fumarate/emtricitabine [TDF/FTC] (Brand Name

Truvada) or tenofovir alafenamide/emtricitabine [TAF/FTC] (Brand Name Descovy) as PrEP (Pre-exposure Prophylaxis) since their last negative HIV test. Results from a recent study in New York City found that individuals who had taken PrEP in the three months prior to a new HIV diagnosis were significantly more prone than those who never used PrEP (26% vs. 2%; P<.0001) to have resistance mutations (M184I / V / IV / MV) to lamivudine/emtricitabine [3TC / FTC] (Brand Name Cimduo) [Misra, et al. 2019]. For these patients, the initial regimen should consist of an integrase strand transfer inhibitor plus a boosted protease inhibitor, and 2 nucleoside reverse transcriptase inhibitors. The initial regimen may be simplified once the baseline genotypic test results have been reviewed.

PREFERRED AND ALTERNATIVE REGIMENS FOR RAPID INITIATION OF ART (RAPID ART)

The following are the preferred and alternative initial regimens for the rapid ART initiation in non-pregnant adults. The regimens are listed in alphabetical order.

Offer ART: Some clinics provide patients with the first dose of ART and a 30-day prescription when the rapid ART initiation protocol is followed [Pilcher, et al. 2017]. Others may provide a 7-14 day ART initiation package or a 30-day prescription.

Table 1: Preferred and alternative regimens for the Rapid ART in non-pregnant adults.

Regimen	Comments	Classification
Preferred regimens		
Tenofovir alafenamide/emtricitabine/bictegravir (TAF 25 mg/FTC/BIC; Biktarvy)	• Available as a single tablet formulation, taken once a day. • TAF/FTC shall not be used in patients with a creatinine clearance (CrCl) <30 ml/min; reassess after the baseline laboratory tests results are available. • It contains 25 mg of TAF, unboosted. • The antacids containing magnesium or aluminum can be taken 2 hours before or 6 hours after BIC. Antacids containing calcium or iron supplements can be taken simultaneously if taken with food.	A1
Tenofovir alafenamide/emtricitabine *and* dolutegravir [a] (TAF 25 mg/FTC *and* DTG; Descovy *and* Tivicay)	• TAF/FTC shall not be used in patients with a CrCl <30 ml/min; reassess after the baseline laboratory tests results are available. • It contains 25 mg of TAF, unboosted. • Two pills once a day. • Antacids containing magnesium or aluminum can be taken 2 hours before or 6 hours after DTG; antacids containing calcium or iron supplements can be taken simultaneously if taken with food.	A1
Tenofovir alafenamide/emtricitabine/darunavir/cobicistat (TAF 10 mg/FTC/DRV/COBI; Symtuza)	• Available as a single tablet formulation, taken once a day. • It contains 10 mg of TAF, boosted. • TAF/FTC shall not be used in patients with a CrCl <30 ml/min; reassess after the baseline laboratory tests results are available. • Pay attention to drug-drug interactions.	A2

Table 2: Regimen for patients with exposure to TDF/FTC as PrEP since their last negative HIV test. Note: The initial ART regimen may be simplified based on the genotypic resistance tests results.		
Dolutegravir and darunavir/cobicistat/tenofovir alafenamide/emtricitabine [a] (DTG/DRV/COBI/TAF/FTC 10 mg/FTC; Tivicay *and* Symtuza)	• TAF/FTC shall not be used in patients with a CrCl <30 ml/min; reassess after the baseline laboratory tests results are available. • Documented DTG resistance after initiation in patients without previous treatment is rare. • Antacids containing magnesium or aluminum can be taken 2 hours before or 6 hours after DTG; antacids containing calcium or iron supplements can be taken simultaneously if taken with food. • Tenofovir disoproxil fumarate (TDF) can be substituted for TAF; TDF/FTC is available as a single tablet (Brand Name Truvada). • Lamivudine (3TC) can be substituted for FTC. • 3TC/TDF is also available as a single tablet.	A3
Table 3: Drugs that should be avoided		
• Abacavir (ABC) = Ziagen • Rilpivirine (RPV) = Edurant • Efavirenz (EFV) = Sustiva	• ABC should be avoided unless the patient is confirmed to be HLA-B*5701 negative. • RPV should ***only*** be administered in patients with a confirmed CD4 ≥200 cells/mm3 cell count and a viral load <100,000 copies/mL. • EFV is not as well tolerated as other antiretroviral drugs and, non-nucleoside reverse transcriptase inhibitors have more resistance rates.	A3

Note:

a. See *Appendix: Use of Dolutegravir in individuals of childbearing age.*

b. Where TAF (Descovy) is mentioned, consider whether TDF (Truvada) is appropriate since this is what is recommended in the DHHS Guidelines and in some specific cases might be considered an option.

Reducing the risk of Mother-to-Child Transmission of HIV requires timely detection of the HIV infection in a pregnant individual and the ART of 3 drugs initiated as soon as possible after the diagnosis. Pregnancy is not a contraindication for rapid ART initiation. Adherence to an ART regimen during pregnancy should be encouraged, as well as the coordination between the HIV and obstetrical care providers (see Prevention of Mother-to-Child Transmission of HIV guideline [NYSDOH AI]).

The table below includes the preferred initial regimens for rapid initiation of ART in pregnant adults.

Table 4: Preferred initial regimens for rapid initiation of ART in pregnant adults.
Also see: DHHS: Recommendations for the use of antiretroviral drugs in pregnant individuals with HIV infections and interventions to reduce Mother-to-Child Transmission of HIV in the United States.

Regimen	Comments	Classification
Tenofovir disoproxil fumarate/emtricitabine and dolutegravir [a] (TDF/FTC *y* DTG; Truvada *and* Tivicay)	• The initial sign of concern for neural tube defects (NTD) with the use of dolutegravir (DTG) during the period prior to conception has substantially decreased. The Panel on HIV treatment during pregnancy and the prevention of Mother-to-Child Transmission of HIV recommends DTG as a preferred drug for pregnant individuals, regardless of the trimester (A2), and for individuals who are trying to conceive (A3) The Panel emphasizes the importance of counseling and informed decision making concerning all ARV regimens for individuals with HIV (A3). • TAF/FTC shall not be used in patients with a creatinine clearance (CrCl) <50 ml/min; reassess after the baseline laboratory tests results are available. • Antacids containing magnesium or aluminum can be taken 2 hours before or 6 hours after DTG; antacids containing calcium or iron supplements can be taken simultaneously if taken with food.	A1
Tenofovir disoproxil fumarate/emtricitabine and atazanavir and ritonavir. (TDF/FTC and ATV and RTV; Truvada and Reyataz, and Norvir)	• TAF/FTC shall not be used in patients with a CrCl <50 ml/min; reassess after the baseline laboratory tests results are available. • Carefully consider drug interactions with RTV. • Scleral icterus of benign hyperbilirubinemia due to ATV may be a concern for the patient. • The recommended dose of ATV is 300 mg once a day during the first trimester; the dose increases to 400 mg once a day during the second and third trimesters when used along with TDF or an antagonist of the histamine-2 receptor. • This regimen can be initiated in the first trimester.	A2
Tenofovir disoproxil fumarate/emtricitabine and dolutegravir and ritonavir (TDF/FTC *and* DTG; Truvada, Prezista *and*	• A DRV/RTV dosage is recommended twice a day (DRV 600 mg plus RTV 100 mg with food) during pregnancy. • TAF/FTC shall not be used in patients with a CrCl <50 ml/min; reassess after the baseline laboratory tests results	A2

Norvir)	are available. • A DRV/RTV dosage is recommended twice a day (DRV 600 mg plus RTV 100 mg with food) during pregnancy. • The regimen can be initiated in the first trimester.	
Tenofovir disoproxil fumarate/emtricitabine and raltegravir (TDF/FTC *and* RAL; Truvada and Isentress)	• RAL 400 mg twice a day is recommended during pregnancy, *not* RAL HD once a day. • TAF/FTC shall not be used in patients with a CrCl <50 ml/min; reassess after the baseline laboratory tests results are available. • Administer as TDF/FTC once a day and RAL 400 mg twice a day. • The recommended dose for RAL is 400 mg twice a day regardless of food. • This regimen can be initiated in the first trimester.	A2

Note:
a. *See Appendix: Use of Dolutegravir in individuals of childbearing age.*

RAPID ART INITIATION COVERAGE

The lack of health insurance coverage for antiretroviral therapy (ART), screening coverage, laboratories, high co-payments, or large out-of-pocket expenses may represent significant barriers for the rapid initiation of ART for some patients. Addressing the financial requirements for ART initiation and helping patients to identify payment assistance resources is an essential component of the rapid ART initiation protocol, to cover necessary drugs, laboratories and/or required tests. Options for Puerto Rico residents, regardless of their immigration status, are described below.

Organizations that receive funding from the *Ending the HIV Epidemic in the U.S.* (EHE) initiative under the Outpatient Medical Services category of the Ryan White Part A program affiliated to the Metropolitan Area of San Juan (EMA San Juan) are covered for drugs and laboratories for rapid initiation of ART under this category.

Partial coverage or uninsured

The **drugs and laboratory tests** may be covered through:

- The outpatient medical services category of the *Ending the HIV Epidemic in the U.S. (EHE)* initiative.
- *Program Income* from organizations participating in the 340b Drug Pricing Program or other sources of unrestricted fund raising or for these purposes.
- Drug samples and/or drug access programs offered by pharmaceutical companies.

Covered by health insurance

Individuals with insurance coverage may be eligible for drug assistance and co-payments to cover the cost of out-of-pocket expenses.

1. For dolutegravir (Tivicay): https://www.myviivcard.com/ .
2. For emtricitabine, tenofovir disoproxil fumarate, bictegravir (Byktarvy): https://www.gileadadvancingaccess.com/get-started-avance-acceso .
3. For darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza): https://www.janssencarepath.com/patient/symtuza/cost-support.

Once ART has started, treatment continuity options will be assessed. These options may include:

- Ryan White Programs (Part A, Part B/*AIDS Drug Assistance Program* [ADAP] Parts C and D)
- Private medical plans,
- Drug access programs from pharmaceutical companies,
- Other federal or state drug access programs,
- Doctor access programs of non-profit organizations or entities.

Rapid ART initiation follow-up

Standard good practice is to do a follow-up by phone, video call or in-person within the first to third day after the individual starts the ART, to assess the side effects, answer questions and promote adherence. If possible, based on the clinic protocol and the individual needs of the patient, an in-person follow-up visit with a healthcare provider is recommended within 7-14 days after ART initiation. If an in-person visit is not possible, then a follow-up by phone, telemedicine or even home visits are recommended.

Once the laboratory tests results are available, ART must be discontinued if HIV diagnosis is not confirmed. If that is the case, the patient may be assessed or referred for PrEP if there is a continued risk of HIV exposure. If HIV diagnosis is confirmed, the ART regimen can be adjusted if necessary (for example, due to a serious kidney disease). Additional adjustments may be required if major resistance mutations are found that would compromise the efficacy of the initial regimen. Arrangements should be made for a viral load test 4 weeks after the ART initiation to evaluate adherence and solve any issues related to treatment maintenance.

Compliance with confidentiality, privacy and informed consent protocols

We recommend updating all necessary protocols and procedures to ensure that Rapid ART is included in all existing protocols in the organizations regarding confidentiality, privacy and informed consent. All participants must be properly guided and all existing and necessary consents must be completed.

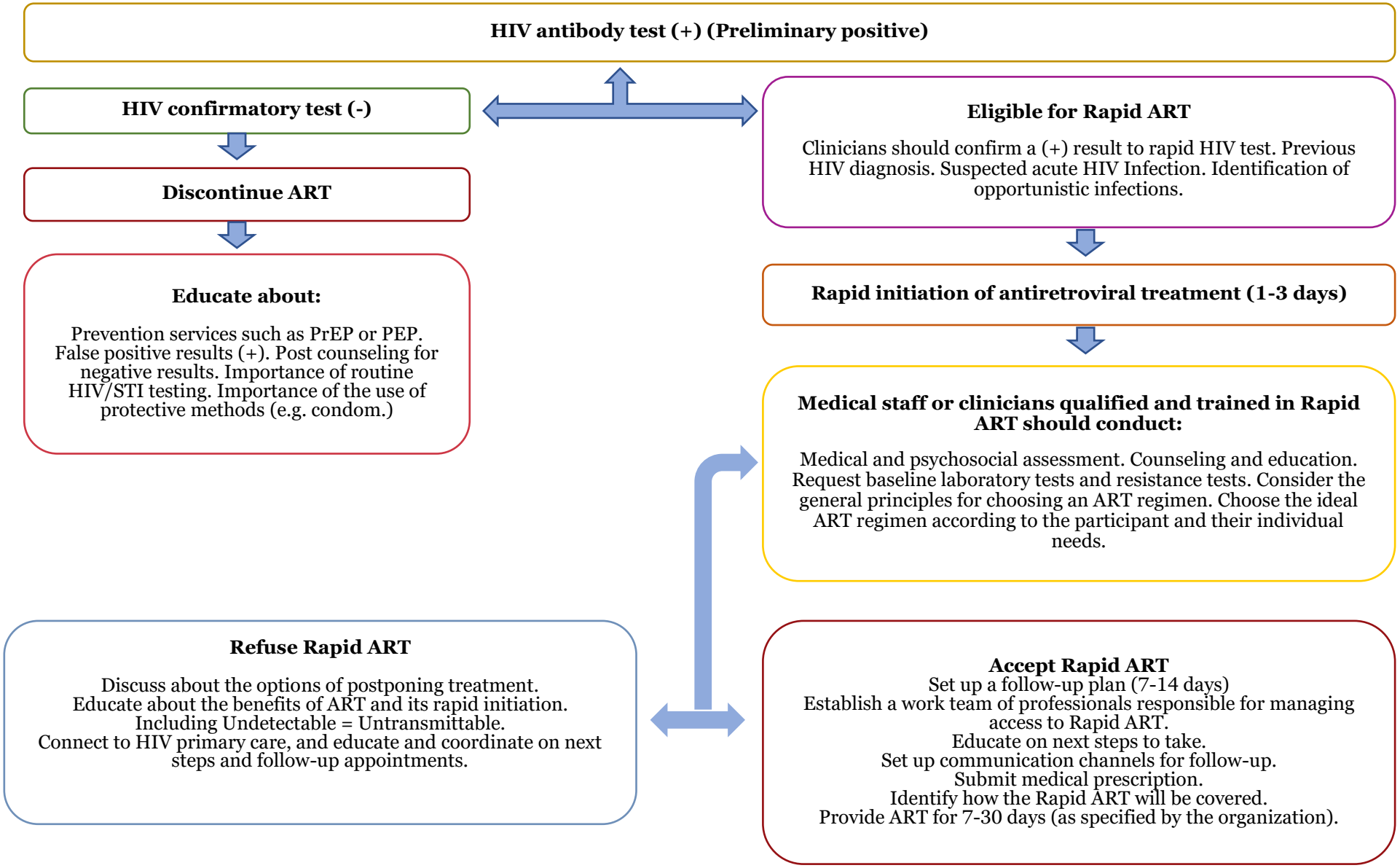
Consultations with Expert Panel

A group of professional experts will be available for consultation during the guidance and implementation period of this protocol for approximately 3 months. These consultations will be documented in a Questions and Answers sections to answer frequently asked questions that could be considered as Best Practices.

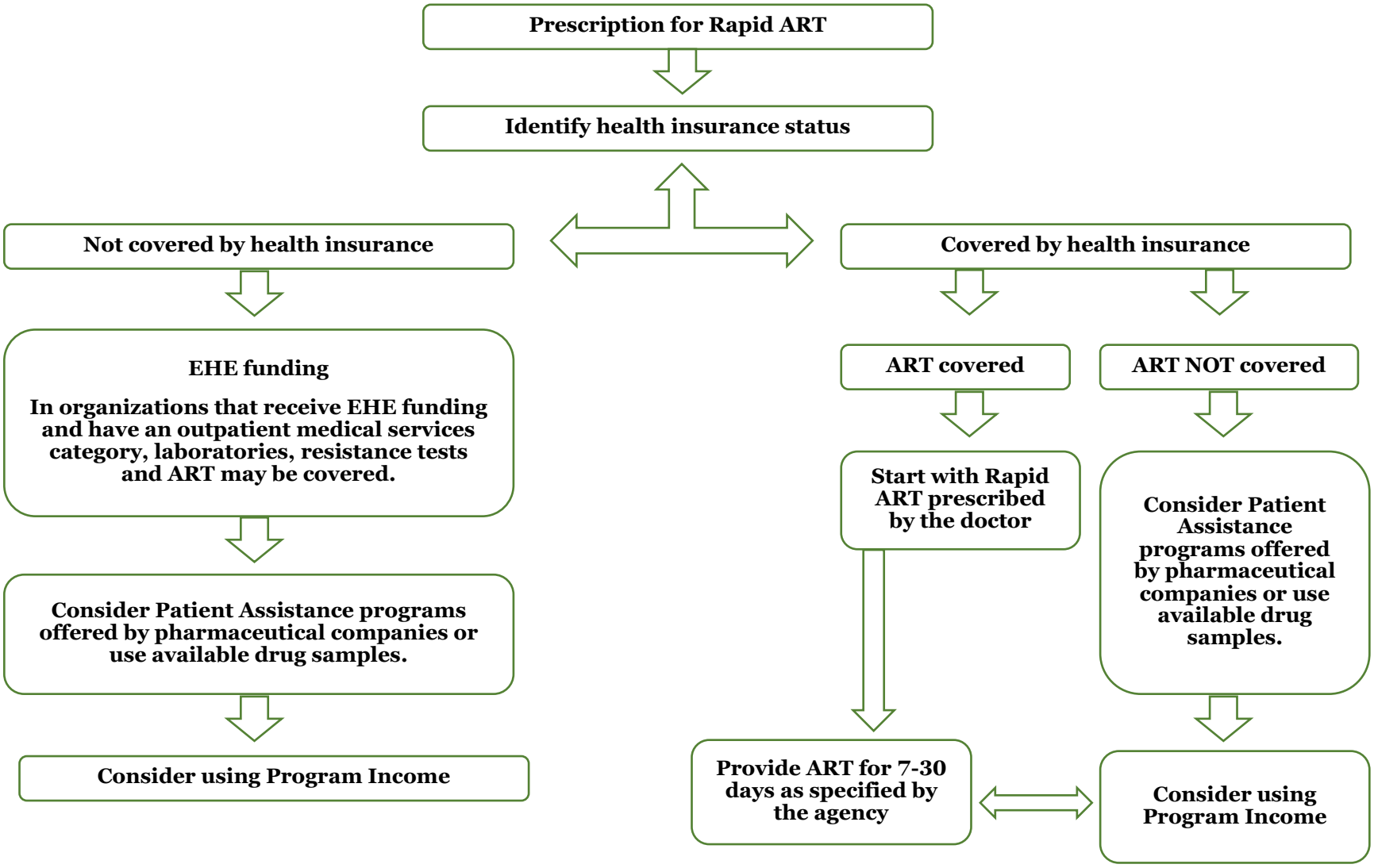
Note: TIES project shall consult with the doctors who will be available for consultation and collect their contact information, the procedure for consultations and the channels though which these consultations may be made.

Consultation Channels: CAN (Community Health (other jurisdictions that are already implementing Rapid ART), CAI (Cicatelli Associates, Inc.), AETC and/or HIVTMD.

RAPID ART FLOW CHART



RAPID ART COVERAGE FLOW CHART



Appendix: Use of Dolutegravir in Individuals of Childbearing Capacity

Lead author: Geoffrey A. Weinberg, MD, with the Medical Care Criteria Committee, May 2021

Evidence from multiple studies indicates no difference in rates of total birth defects among infants exposed to antiretroviral (ARV) medications during the first trimester compared with infants exposed later in pregnancy. ARVs are generally considered safe and may be taken by pregnant patients with HIV without increasing the risk of infant birth defects. The MCCC is providing the following updated information for medical care providers concerning preliminary reports that previously had linked dolutegravir (DTG) to neural tube defects (NTDs) in infants exposed to dolutegravir during the periconception period [Zash, et al. 2018; Zash, et al. 2019; Reefhuis, et al. 2020].

Potentially increased NTDs and DTG: NTDs are birth defects, including meningomyelocele and spina bifida, thought to occur early after conception during development of the embryonic neural tube. The neural tube closes by approximately 8 weeks gestational age, which is 8 weeks after the last menstrual period or approximately 6 weeks post-conception.

Ingestion of folic acid or folate by a pregnant individual significantly lowers the rate of NTDs; all individuals in the United States who are pregnant or trying to conceive and engaged in prenatal care are routinely administered 400 µg of folic acid daily. The background rate of NTDs in the general population in the United States and other countries that routinely fortify food with folate or folic acid is low: approximately 0.07% of all births (7/10,000 births) [Reefhuis, et al. 2020].

In 2018, an unplanned interim analysis of a large observational clinical trial conducted in Botswana, a country where food is not routinely fortified with folate or folic acid, was performed. The researchers found NTDs in 0.94% of 426 infants exposed at conception to maternal DTG-based antiretroviral therapy (ART) compared with 0.12% of 11,300 infants exposed to non–DTG-based ART. Importantly, however, as more data were collected, the rates of infant NTDs markedly declined [Zash, et al. 2018; Zash, et al. 2019; Antiretroviral Pregnancy Registry Steering Committee 2020; Zash 2020; DHHS 2021]. The latest available data, through April 2020, now show that the rate of infant NTDs with maternal DTG-based ART use at conception is not any greater than it is in infants exposed to non–DTG-based ART at conception: 0.19% [Antiretroviral Pregnancy Registry Steering Committee 2020; Zash 2020; DHHS 2021]. No increases have been found in the registry data or through pharmacovigilance database studies from Europe and the United States [Vannappagari and Thorne 2019; van De Ven, et al. 2020]. Nor have any differences been found in the rates of NTDs among infants in a randomized controlled open-label phase 3 trial of DTG-based versus EFV-based ART in pregnant individuals, though the median gestational age at enrollment in this trial was 22 weeks, and all enrollees were at 14 weeks or more gestational age at enrollment [Lockman, et al. 2021].

Benefits of DTG: There are many known benefits of DTG as a component of ART for all adults, pregnant or not, and many children. DTG is potent, rapidly reduces viral load, has a high barrier to HIV genetic resistance, and is generally well- tolerated. Moreover, folate deficiency is uncommon in countries such as the United States. Thus, both the U.S. Department of Health and Human Services and the World Health Organization consider DTG a preferred ARV drug for

individuals with HIV in all trimesters of pregnancy, and those with HIV who are trying to conceive. If an alternative ART regimen that does not include DTG is the best choice, alternatives to DTG during pregnancy include raltegravir, ritonavir- boosted atazanavir, or ritonavir-boosted darunavir (see the NYSDOH AI guideline Selecting an Initial ART Regimen > Specific Factors to Consider and Discuss With Patients). No data currently exist to support the use of bictegravir during pregnancy or the period surrounding conception. Further, cobicistat-boosted regimens containing elvitegravir, darunavir, or atazanavir are not recommended due to reduced levels of the integrase inhibitors given with cobicistat during pregnancy.

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