UCSF Division of HIV, Infectious Diseases & Global Medicine
Department of Medicine

ZUCKERBERG SAN FRANCISCO GENERAL
Hospital and Trauma Center

SAN FRANCISCO GENERAL HOSPITAL "RAPID" ANTIRETROVIRAL THERAPY

STANDARD OPERATING PROCEDURES

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I. INTRODUCTION

"RAPID" (Rapid ART Program Initiative for HIV Diagnoses) is a clinical program of the Division of HIV, Infectious Diseases and Global Medicine at Zuckerberg San Francisco General Hospital ("Ward 86"). The goal of RAPID is to provide immediate ART to all HIV-infected patients to benefit their health. The RAPID program extends the concept of universal ART to include immediate linkage to HIV care and initiation of ART. The SFGH RAPID program was established at SFGH in 2013 and now is a component of the city-wide RAPID initiative launched with the 2015 San Francisco city Getting to Zero strategic plan.

II. PURPOSE OF THIS DOCUMENT

1. To provide the medical and public health rationale for RAPID
2. To describe the medical, counseling, and care planning components of the SFGH RAPID program
3. To describe evaluation metrics for RAPID

III. RATIONALE FOR RAPID

Rapid ART initiation may confer compelling benefits conferred to the individual with new diagnoses of HIV. RAPID also brings a community level public health benefit by reducing the risk of HIV transmission. We highlight here benefits of immediate and universal ART.

III.A. Individual patient benefits:

There are increasing data showing that there may be direct benefits to the individual patient if ART is initiated immediately, particularly during acute/early HIV infection. This means not waiting a few days or weeks between HIV diagnosis and starting antiretroviral therapy. These benefits are summarized below.

III.A.1. Viral load suppression is not sufficient to restore immunologic health.

- Initiating ART during chronic HIV infection is associated with dampened CD4+ T cell recovery. In one study, 25% of patients who start ART at CD4+ T cell counts <200 cells/mm^3 were unable to achieve CD4+ T cell counts >500 cells/mm^3 even after >7 years of suppressive ART[1].
- The inability to restore a normal CD4+ T cell count in the setting of ART is associated with an increased risk of AIDS- and non-AIDS related complications, and this risk persists even with restoration of CD4+ T cell counts above 500 cells/mm^3[2-4].

III.A.2. Initiating ART during acute/early infection may improve CD4+ T cell recovery and decrease the overall size of the HIV reservoir.

- When ART is initiated during chronic HIV infection, there is ongoing low-level viral replication detected by sensitive assays despite long-term, suppressive ART[5-7].

- Earlier initiation of ART during acute HIV infection may lead to improved CD4+ T cell count recovery, decreased on-treatment immune activation, and decreased HIV reservoir size[8].
- In some individuals, early initiation of ART during acute HIV infection may lead to prolonged control of HIV after the subsequent cessation of ART[9].
- Immediate initiation of ART during extremely early HIV infection (Fiebig Stages I-III) may protect long-lived central memory CD4+ T cells from becoming infected and decrease the size of the long-term reservoir[10,11, 12].

III.A.3. Immediate initiation of ART may improve linkage to care and retention in care. In our experience, most patients, when provided with the opportunity to start ART, choose it. Community awareness about universal ART means that many newly diagnosed HIV+ patients come in expecting and wanting to start medications. And many patients report that deciding to start ART and rapidly achieving viral suppression provides them with the first experience of feeling empowered to successfully live with HIV.

- The lack of immediate access to HIV Care and Treatment has historically been a barrier to HIV testing, linkage to care, ART initiation, and retention in care.
- Accumulating data suggest that reducing the time from HIV testing to ART initiation enhances retention in care and has no detrimental effect on HIV clinical outcomes.

III.A.4. In a pilot study of RAPID at Ward 86, immediate ART was highly acceptable to patients and providers, significantly reduced time from diagnosis to undetectable viral load, and was associated with very high rates of linkage to and retention in care[13].

- Analysis of the first 39 RAPID patients vs. 47 patients treated using standard of care (universal ART) shows the following:
  - Shorter time to virologic suppression using the RAPID protocol (56 days) vs. universal ART (132 days) (p value<0.001)
  - High retention in care among RAPID participants 90% at 6 months (RAPID) vs. 85% (Universal ART)
  - 100% patient acceptance of immediate ART vs. 85% (Universal ART)
  - High provider acceptance of RAPID

III.A.5

A multisector initiative in San Francisco (Getting to Zero San Francisco) to prioritize RAPID ART initiation in newly-diagnosed HIV+ individuals (as part of an overall effort to improve HIV prevention and care) resulted in significant decreases in time from HIV diagnosis to ART initiation and to virologic suppression in the years studied, 2013-2016[14]:

- Time from HIV diagnosis to first HIV care visit decreased from 8 days to 5 days
- Time from 1st HIV care visit to ART initiation decreased from 27 days to 1 day
- Time from HIV diagnosis to HIV suppression to <200 copies/mL decreased from 134 days to 61 days

III.A.6 Demonstration projects of rapid ART initiation in 2 United States settings have shown decreases in time to ART start and to first virologic suppression[15.16]. Randomized clinical trials of immediate ART done in developing world settings have shown that immediate ART at diagnosis (compared with starting according to the local standard of care) has been shown to increase rates of linkage to care[17], ART initiation[18] and reaching first virologic suppression[17,18]; to increase retention with virologic suppression, and reduce mortality.[19] The World Health Organization now recommends offering immediate ART to all persons newly diagnosed with HIV[20].

The 2018 Guidelines of the International AIDS Society-USA support immediate ART initiation[21].

III.B. Public health benefit:

Earlier ART initiation and earlier viral load suppression will likely decrease the risk of subsequent HIV transmission events[22]. This is particularly true for patients who are in the acute stages of HIV infection.

IV. ELIGIBILITY FOR RAPID

- Newly diagnosed HIV patient (inclusive of acute and chronic infection)
- Persons with discordant HIV testing (eg, Ag/Ab test positive and differentiation test negative or indeterminate, or Ag/Ab negative but HIV RNA detectable) if there is a suspicion of acute HIV infection
- Patient re-engaging in HIV care with low CD4 cell counts (<200 and/or significant co-morbidities)

V. OPERATIONS

V.A. Overview

The operations of the RAPID program allow for an accessible HIV health team to see a newly diagnosed (or newly reengaged) patient on the same day as their diagnosis, offer therapy, and put a counseling and sustainable care plan into action. Generally, a new HIV diagnosis is made through a San Francisco Community HIV testing site or in a medical setting such as primary care, emergency department or urgent care, specialty clinics (methadone, TB, prenatal, renal), inpatient hospitalization, or psychiatry. Our Testing and Linkage to care team (PHAST) is paged either by the community testing site or by the San Francisco General

Hospital Clinical Laboratory, via pager Monday-Friday 8-5pm, for any HIV+ antibody (or antigen/antibody) test result or a detectable HIV RNA level in the absence of an HIV+ antibody test result. Determination is then made whether the diagnosis is a new diagnosis and whether it is likely to be an acute infection. After receiving test result disclosure and post-test counseling at the testing site, patients are invited to the San Francisco General Hospital Ward 86 RAPID program. Upon arrival, the patient is welcomed and meets with a social worker for additional post-test counseling and education as well as psychosocial assessment and initiation of insurance paperwork. Then the patient meets with the RAPID provider for further counseling and ART initiation. The majority of RAPID occur on weekday afternoons, and are expected to last 1-2 hours.

V.B. The Initial "RAPID" visit (Day 1):

V.B.1. Counseling: A key component of the RAPID program is to ensure that the patient has individualized post-test counseling and education. This includes but is not limited to discussion of the patient's new HIV diagnosis, psychosocial assessment/intervention, discussion of risks/benefits of treatment, and education on HIV and safer sex practices. At that time, assessment is started to identify potential barriers to successful linkage to care (medical insurance including drug benefits, mental health, substance use, unstable housing, immigration status, legal challenges). The initial session also addresses partners at risk.

What is different about the RAPID program is that instead of performing all the counseling up front before therapy starts, the counseling starts on the same day as treatment initiation, and continues after a patient is started on treatment. With this approach, all the standard individualized counseling components are covered, but they a) do not delay therapy initiation and b) offer the opportunity to continue counseling while the patient is starting therapy.

V.B.2. Establishing a sustainable long-term care plan: Successful outcomes in HIV depend not only on the rapid initiation of therapy but also on the rapid establishment of a sustainable HIV care plan. Based on the initial assessment of potential barriers to successful linkage to care, a plan is put in place with the RAPID team social worker to address both immediate and long term barriers. This may include emergency housing, emergency access to insurance and drug benefits, expedited access to mental health services or residential drug treatment programs, counseling and referrals to address immigration or other legal issues. All patients receive an assessment of the impact of HIV stigma and how they will cope with this as well as whether they will need additional resources (support groups, ability to meet with an HIV+ peer advocate, counseling, etc.). In addition, discussion is initiated about current and recent sexual partners and other persons at risk for infection such as children or persons with whom they share IV drugs and drug paraphernalia. A plan is formulated for disclosure and testing of persons at risk. Patients are counseled that they will be contacted by the Department of Public Health Partner Services branch.

Based on the identification of barriers to linkage and retention in care, a contingency plan is identified for potential problems such as missed appointments, missed dosages of ART, inability to fill medications at the pharmacy, etc. Patients are given clear guidance on how to get help and support and remain connected to the clinic.

V.B.3. Medical Evaluation:

HIV history: An HIV risk/prevention history will be taken and recorded, including:

1. HIV testing history and date of last negative HIV test
2. PrEP use
3. PEP use
4. Sexual practices and serostatus of partners, if known
5. Injection drug use and practices; and serostatus of partners, if known

Medical history: A full medical history will be taken, particularly since patients will be started on ART before most laboratory test results have returned:

1. Co-morbidities (especially kidney and liver problems)
2. Medications
3. Drug allergies
4. Review of systems (to alert for the presence of OIs or seroconversion syndrome)

Laboratory studies: As part of standard intake labs, all newly diagnosed patients will have the following laboratory tests performed on the day of the initial RAPID visit: HIV antigen/antibody (4^{th} generation assay), HIV viral load, HIV genotype (including integrase genotype), CD4+ T cell count, HLA-B5701 polymorphism testing, comprehensive metabolic panel (including creatinine and liver function tests), RPR, HAV IgG antibody, HBsAg, HBcAb, HBsAb, and HCV antibody. Quantiferon, Toxoplasma IgG antibody, and G6PD testing may also be considered.

ART counseling on the risks and benefits of immediate ART: A full discussion occurs with the patient regarding the potential benefits and risks of immediate ART. The role of viral load monitoring will also be included in this discussion to introduce the concept and therapy goals. Patients are told about the possibility of developing an immune reconstitution syndrome. They are also reminded about the importance of being in close contact with the health system during the early months of treatment should any complications arise related to medications or to HIV disease. Emphasis is placed upon listening to patient concerns, and conveying to the patient that they will likely have additional questions through this process that the team is ready to address.

V.B.4. Initiation of immediate ART:

- The provider reviews with the patient his/her plan for long-term ART and follow-up care.
- Unless there is a clear contraindication or the patient declines, the provider selects (in consultation with the patient) and prescribes an ART regimen. If starter packs of ARV medications are available, the patient is given a starter pack and takes the first dose of ART at that time.

Selection of Antiretroviral Therapy: The selection of a particular ART regimen for an individual patient will be guided by the patient's preferences, co-morbidities, potential drug interactions, and drug allergy history. Most RAPID patients will be initiated on ART before the results of laboratory tests are available (e.g., HIV viral load, genotype, creatinine, liver function tests, hepatitis B status, HLA-B5701). Thus, regimens for RAPID ART should be effective in a broad range of clinical situations, at least in the short period until lab results are available and regimens can be modified if needed. RAPID ART regimens should be potent even at high HIV RNA levels and have a high genetic barrier to resistance (in case some level of transmitted resistance is present). Ideally they also are tolerable, easy to take, and involve few pills.

Our **preferred** RAPID ART regimen for most patients, based on these criteria and our RAPID clinical experience, as well as pragmatic cost issues (eg, purchase of ARVs for RAPID starter packs) is:

- Dolutegravir[a], 50 mg once daily + (tenofovir alafenamide [TAF]/emtricitabine [FTC] or tenofovir disoproxyl fumarate [TDF]/FTC[b]), 1 tablet once daily

The following also are **reasonable options**, though may have less supporting data or clinical experience for use in RAPID ART, more potential adverse effects, or higher costs:

- Bictegravir/TAF/FTC, 1 tablet once daily
- Darunavir/cobicistat/TAF/FTC, 1 tablet once daily
- Darunavir 800 mg once daily + ritonavir 100 mg once daily + (TAF/FTC or TDF/FTC[b]) 1 tablet once daily

These **alternatives** may be considered if access to the above regimens is limited:

- Elvitegravir/cobicistat /TAF/FTC, 1 tablet once daily
- Raltegravir 1200 mg once daily + (TAF/FTC or TDF/FTC[b]) 1 tablet once daily)

[a] Dolutegravir recently has been associated with a higher risk of neural tube defects in infants born to women who were taking dolutegravir at the time of conception. For women of childbearing age who may become pregnant while taking dolutegravir (ie, have male sex partners and are not using effective contraception), the FDA currently recommends that providers discuss risks and benefits of dolutegravir and alternative ARVs, and consider alternatives.

[b] Tenofovir alafenamide (TAF)/emtricitabine is preferred (except in pregnant womean), but tenofovir disoproxil fumarate (TDF)/emtricitabine may be used instead.

For Pregnant Women*, the following RAPID ART regimen options are recommended:

<8 weeks from last menstrual period:

- Darunavir 600 mg twice daily + ritonavir 100 mg twice daily + TDF/FTC 1 tablet once daily (consider addition of raltegravir 400 mg twice daily for faster reduction in HIV RNA)
- Raltegravir 400 mg twice daily + TDF/FTC 1 tablet once daily

≥8 weeks from last menstrual period:

- Darunavir 600 mg twice daily + ritonavir 100 mg twice daily + TDF/FTC 1 tablet once daily (consider addition of dolutegravir 50 mg once daily for faster reduction in HIV RNA)
- Dolutegravir 50 mg once daily + TDF/FTC 1 tablet once daily
- Raltegravir 400 mg twice daily + TDF/FTC 1 tablet once daily

*TAF, bictegravir, and elvitegravir/cobicistat/TAF/FTC are not currently recommended in pregnancy. Dolutegravir is not recommended at the time of conception or the first 8 weeks of pregnancy.

The following **should NOT be prescribed** for RAPID ART:

- Abacavir (results of HLA B5701 testing will not be available, and risk of abacavir hypersensitivity reaction in persons with HLA B5701 allele is substantial)
- NNRTIs (results of pre-treatment genotype will not be available and likelihood of transmitted NNRTI mutation is relatively high)

Individual ART regimens may need to be tailored for patients who have had recent PrEP or PEP exposure, or a source partner with known viral resistance (for example, a 3-class regimen that includes an integrase inhibitor, a protease inhibitor, and NRTIs may be indicated, pending the patient's genotype results). They may also need to be tailored for a patient with known renal disease.

Selected ARVs must be covered by the patient's insurance plan and available in the patient's pharmacy.

V.B.5. Prescription of Antiretroviral Medications

- Once an ART regimen has been selected, the health care provider creates an order (prescription) for a standard 30-day supply of the medication(s) and faxes it to the appropriate pharmacy (and records the order in the medical record).
- The patient is advised to go to the pharmacy directly to be sure his/her ADAP/insurance is active and that the pharmacy is able to supply a standard monthly supply. The patient is instructed to call the Ward 86 social worker immediately if there are problems with obtaining the medication (e.g., issues with insurance coverage). For patients who (with the help of our social workers) are applying for/establishing emergency access to insurance, we preferentially use pharmacies that are able to process the new insurance information rapidly.
- The patient is encouraged to take the first dose of ART that same day, if he/she has not already taken the first dose in clinic.

V.C. Follow-up RAPID visits

V.C.1. **Day 2:** The social worker calls the patient on the day after ART initiation to provide psychosocial support, assess for any clinical symptoms or medication side effects,

and provide any support for the patient to fill his/her long-term ART prescription. This may involve contacting the patient's pharmacy to work out any potential problem with access to medications. Any medical symptoms or questions are conveyed to the provider for the appropriate follow-up.

V.C.2. **Day 5-10:** The patient has an appointment with a medical provider who provides follow-up on clinical care and laboratory tests that are ordered. At that visit, CD4+ T cell count, HIV RNA, and HLA-B5701 results are reviewed with the patient. Assessment is made for HIV symptoms or medication side effects. Treatment may be adjusted as appropriate. Care is then transitioned to a permanent provider, preferably the same one who saw the patient as the RAPID provider, for routine primary HIV care.

V.C.3. **Ongoing:** Access to social workers is provided during this time period and over the next 3 months to continue working on the stabilization plan, and to provide ongoing support and education for coping with stigma, partners/family/friends disclosure and other barriers (e.g., mental health, substance use, housing, immigration, insurance). Patients are offered a session with a Clinical Pharmacist to support adherence and provide additional education on ART.

Appointment reminders are made and immediate follow-up for any missed appointment is done, including outreach and home visits.
For patients deemed at continued risk for poor retention in care, referrals are made to case managers and overlapping support is provided until patient has established a relationship with the case manager.

VI. OPERATIONAL DEFINITION OF TERMS RELATED TO ENGAGEMENT IN HIV CARE

All patients start as "active patients." After 6 months, they may progress to "engaged" patients where viral suppression is achieved, care plan is established, and psychosocial needs have stabilized. Patients who transfer to another system are classified as "transferred patients." Patients for whom no information or contact can be gained are classified as "Lost to follow-up."

ACTIVE PATIENTS: These patients have maintained linkage to the clinic either through primary care or urgent care and continue to need support (appointment reminders, follow-up on missed appointments, nursing care coordination, education regarding medication refills, scheduling, psychosocial stabilization, appropriate utilization of urgent care or emergency services); this includes all patients newly enrolled (within past 6 months).

ENGAGED PATIENTS ("HIV CARE ENGAGEMENT"): Engaged in HIV care for at least 6 months; health insurance established; plasma HIV-1 RNA below the level of quantitation (e.g., < 40 copies/mL) for at least 3 months on ART; demonstrated ability to maintain engagement in primary care independently including scheduling and rescheduling appointments, refilling medications, and utilizing urgent care and emergency services appropriately; attended at least 3 primary care appointments; filled and refilled long-term ART prescriptions; have a self-identified medical home.

TRANSFERRED PATIENTS: Includes patients admitted to Laguna Honda Hospital or any other skilled nursing facility, or any community hospice programs; patients who become incarcerated; patients who chose to transfer their care to a clinic in or out of county; patients with insurance change that mandates care transfer.

LOST TO FOLLOW UP PATIENTS: Have made no contact with long-term HIV provider during the past 6 months, and no contact information exists after verification of lost contact with San Francisco DPH Surveillance.

LINKAGE TO CARE: One initial medical encounter post HIV diagnosis, with baseline HIV laboratory testing and assignment of ongoing primary care (medical home + primary care provider).

VII. METRICS AND OUTCOMES

VII.A. Baseline information: The following information is recorded at the time of RAPID referral for tracking purposes:

VII.A.1. Information on the referral:

- Locations of testing, disclosure, and referral
- Type of referral (on-campus inpatient/on-campus ambulatory clinic/off-campus clinic or private MD/testing site/jail or prison)
- New diagnosis/first initiation of care?

VII.A.2. Prior engagement in medical care

- Insurance status
- Identified primary medical provider
- Identified HIV care or PrEP provider

VII.A.3. Clinical characteristics:

- HIV stage on date of referral, as determined by testing history (acute/non-acute/AIDS)
- PrEP or vaccine use
- Presence of active opportunistic infection
- Presence of medical contraindications to immediate ART start (per medical provider)
- CD4+ T cell count and HIV RNA viral load at ART start date

VII.A.4. Demographics

- Age
- Race/ethnicity
- Sex and gender

VII.A.5. Presence of major mental health disorders

VII.A.6. Active substance use

VII.A.7. Housing status (stably or unstably-housed, homeless, residential treatment, incarcerated)

VII.A.8. Immigration status

VII.B. Outcomes: Outcomes data are collected to assess program performance and impact. They are summarized overall and according to specific patient categories above.

VII.B.1. Time to specific milestones. RAPID tracks dates at which each patient achieves specific care milestones. This allows analysis of the time delays that occur at each step of the disclosure, referral, linkage. and engagement process. Dates for the following milestones are collected (they need not occur in order):

- First positive diagnostic test
- Test result disclosure
- Clinic contact/referral
- First kept clinic visit
- First clinic medical provider visit
- First kept clinic visits with:
  - Mental health provider if applicable
  - Substance use counselor if applicable
  - Clinic-assigned primary medical provider
- Number of missed appointments
- First ART prescription date (after diagnosis of infection)
- First viral load suppression <1500, <200 and <50
- Achievement of specific milestones
- Linkage to ward 86 (program definition) within 1, 3, 6 or 12 months
- Engagement in care (program definition) within 12 months
- Viral suppression <200 and <50 by 3, 6 and 12 months

VIII. FAQs

- ***Should a patient wait to start ART until a relationship with a long-term HIV provider has been established?*** The RAPID program places greatest importance on the benefit to the patient of starting therapy immediately, receiving psychosocial support, and establishing a care plan. This means that for patients who do not have an established health care provider, the initial RAPID visit may be conducted by a provider for whom a long term relationship has not been established. This situation is similar to initiation of treatment for HIV or any disease that occurs in the hospital.

- ***Should providers wait for genotype results before ART initiation?*** For patients who are newly diagnosed with HIV, genotypes are essential for patient management. However, in most cases treatment can safely be started before the genotype result is back and then an ART regimen can be modified as needed. We perform a baseline genotype test followed by immediate ART initiation (without waiting for genotype results). We have selected certain ART regimens as preferred RAPID regimens for newly diagnosed patients, with the knowledge of current rates of transmitted drug resistance in San Francisco. However, individual ART regimens may need to be tailored for patients who have had recent PrEP or PEP exposure, or who had a transmission partner with drug-resistant HIV. For patients who are re-engaging in care and have complex ART histories, there may be circumstances where the provider chooses to wait for the genotype result before re-initiating therapy.
- ***Should providers wait for psycho-social stabilization before ART initiation?*** Patients with untreated mental health, active substance use, immigration issues, and/or marginal housing face considerable barriers to successful adherence and linkage to care. That being said, they deserve the highest standard of HIV care which includes immediate ART initiation. Often, a RAPID visit is the first time that a patient has come into contact with an integrated model of care which will address both their medical as well as their psycho-social needs. In addition, it is accepted that providers are generally not good at judging whether or not their patient will be adherent. With appropriate counseling and contingency management combined with careful selection of an ART regimen with less potential for resistance, all patients can have a chance at achieving viral suppression while working on stabilization to ensure long-term retention.

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