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The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a U.S. Public Health Setting

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Abstract

Background—ART is typically begun weeks after HIV diagnosis. We assessed the acceptability, feasibility, safety and efficacy of initiating ART on the same day as diagnosis.

Methods—We studied a clinic-based cohort consisting of consecutive patients who were referred with new HIV diagnosis between June 2013 and December 2014. A subset of patients with acute or recent infection (<6 months) or CD4<200 were managed according to a “RAPID” care initiation protocol. An intensive, same-day appointment included social needs assessment; medical provider evaluation; and a first ART dose offered after labs were drawn. Patient acceptance of ART, drug toxicities, drug resistance and time to viral suppression outcomes were compared between RAPID participants and contemporaneous patients (who were not offered the program), as well as with an historical cohort.

Results—Among 86 patients, 39 were eligible and managed on the RAPID protocol. 37 (94.9%) of 39 in RAPID began ART within 24 hours. Minor toxicity with the initial regimen occurred in two (5.1%) of intervention patients versus none in the non-intervention group. Loss to follow-up was similar in intervention (10.3%) and non-intervention patients (14.9%) during the study. Time to virologic suppression (<200 copies HIV RNA/mL) was significantly faster (median 1.8 months) among intervention-managed patients when compared with patients treated in the same clinic under prior recommendations for universal ART (4.3 months; p=0.0001).

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Conclusions—Treatment for HIV infection can be started on the day of diagnosis without impacting the safety or acceptability of ART. Same-day ART may shorten the time to virologic suppression.

INTRODUCTION

Early initiation of antiretroviral therapy (ART) reduces morbidity and mortality for patients with HIV infection [1–4], and reduces the potential for HIV transmission by suppressing viral replication [5]. Since 2010, guidelines from the San Francisco General Hospital (SFGH) HIV Clinic ("Ward 86") have accordingly recommended that ART be offered to all patients with HIV infection, regardless of CD4 cell count [6], a practice endorsed nationally in 2012 and worldwide in 2015. Supported by programs promoting linkage to care [7], this "universal ART" approach has been associated with reduction in the time from new diagnosis to virologic suppression in San Francisco [8].

However, structural barriers, patient attitudes and provider attitudes may impede the rapid initiation of HIV treatment. For example, HIV testing often occurs at a site different from that where treatment is initiated, which may result in weeks elapsing before a patient is able to link to HIV care. Additional steps are often required to secure health insurance benefits that will pay for ART, and to schedule and keep appointments with a new primary medical provider able to prescribe it.

Even when HIV care can be initiated in a clinic, other aspects of care are typically prioritized over ART at initial visits. Preparatory laboratory results (which usually include HIV genotyping, hepatitis serologies, etc.) can take weeks to return. In the traditional series of early events involved in linkage-to-care and ART initiation (Figure 1), labs may be drawn at initial visits but other aspects of care such as post-test counseling and education; management of housing and substance abuse problems are prioritized and ART initiation is deferred. In some circumstances, ART may be deferred until patients have "proved themselves ready" to adhere to ART by attending multiple clinic visits.

In 2013, the SFGH HIV clinic launched a clinical health systems intervention entitled RAPID (Rapid ART Program for Individuals with an HIV Diagnosis). This intervention was designed to facilitate ART initiation for patients with new HIV diagnoses, by immediately addressing structural barriers to dispensing same-day treatment. Under the RAPID care model (Figure 1), ART is initiated as soon as possible after HIV status is disclosed and ideally on the day patients are first referred for care—even as other aspects of linkage and engagement are ongoing. In this paper, we evaluated the feasibility, acceptability, safety and efficacy of a health systems intervention to promote same-day, observed ART initiation for HIV infection in a public health outpatient clinic setting.

METHODS

Study design

A clinic-based cohort study measured outcomes among individuals referred to care with a new diagnosis of HIV infection. The primary analysis compared outcomes among patients

who were initially managed according to the RAPID intervention protocol with those managed according to the clinic standard of care over the same time period. A second, pre- and post-intervention analysis compared outcomes in the intervention cohort with outcomes in a retrospective cohort of patients referred in prior years. This retrospective cohort included groups treated in both CD4-guided and universal ART treatment eras. All data were collected by review of electronic medical records. The evaluation was approved by the UCSF Committee on Human Subjects Research (UCSF CHR 12-10141).

San Francisco ART initiation guidelines

San Francisco's "universal ART" era was launched in January 2010 with SFGH HIV clinic and San Francisco Department of Public Health guidelines recommending that ART be offered immediately by primary care providers to all HIV-infected patients [6,9]. Previously, from 2006 through 2009, "CD4-guided" ART was recommended for patients with CD4+ T-cell counts <500 cells/mm^3.

Existing systems for referral and linkage at SFGH

The SFGH HIV Clinic provides outpatient continuity care to approximately 2800 HIV-infected patients. All residents of the County of San Francisco who do not have private health insurance are eligible for HIV care at this clinic. Referrals of new HIV cases come from public testing sites, off-campus clinics around San Francisco, and other outpatient and inpatient wards on the SFGH campus. Since 2002, all patients referred for initial HIV care at the clinic receive support from a multidisciplinary team of social workers, nurses and physicians providing comprehensive client services beginning with their first intake visit (as illustrated in Figure 1). In its standard of care approach, the SFGH HIV clinic team addresses medical (symptoms), social (housing, insurance, food access, immigration status) and psychological (counseling, mental health, substance use) concerns. This approach has been associated previously with excellent rates of linkage to care [7].

Intervention design

According to the novel RAPID care model (illustrated in Figure 1), ART should be initiated as soon as possible after a new diagnosis, preferably on the day of diagnosis, rather than deferred until patients are engaged in primary care. There was no active recruitment. The intervention involved no new procedures at HIV testing sites and no specific coordination with public health investigations. At our clinic, the RAPID program deployed the following intervention components to achieve its aim: 1) *Same-day access to an HIV provider*: patients were provided an appointment with an on-call HIV specialty physician or nurse practitioner on the day of diagnosis. Taxi vouchers were available for immediate transportation from the testing site to the clinic. 2) *Same-day medical visit outline*: During a same-day visit,lasting 3–4 hours, the prescribing provider provided education regarding HIV infection, risk reduction and sexual health, and benefits of ART with the patient. Possible contraindications to ART were assessed and the patient was given the option to decline treatment. Baseline laboratory tests (CD4 cell count and HIV RNA level, renal and liver function tests, hepatitis serologies, HLA B5701 testing, HIV resistance genotyping) were ordered but not typically available prior to ART start. 3) *Accelerated insurance approval process* Pre-existing, available protocols for emergency drug assistance in San Francisco were immediately

activated and follow-up of applications prioritized. 4) *Pre-approved regimens*: ART regimens that could be used without the results of genotyping or lab testing had been pre-approved by a local expert committee accounting for patterns of transmitted drug resistance and drug toxicity (e.g., dolutegravir and tenofovir disoproxil plus emtricitabine was approved and commonly used due to low prevalence of transmitted resistane to tenofovir and dolutegravir in SF). 5) *5-day starter packs*: Starter packs for each pre-approved regimen were available if needed for the participant to initiate ART while insurance benefits were being arranged (if benefits were in place, multiple dose starter packs were not necessarily provided). 6) *Observed administration of a first dose:* Patients accepting ART were offered the first dose in the clinic, with the provider in the room for support. 7) *Telephone follow-up:* RAPID nurses contacted patients within the first 7days to review lab results, inquire about adherence, pharmacy/prescription issues, and possible side effects. The timing of initial follow-up was guided by provider concern, and varied from 1–7 days.

Inclusion of new clinic patients in the intervention program

Between July 2013 and January 2014, RAPID was targeted to patients known at the time of referral as having *acute or recent HIV infection*, defined by having an HIV negative test within 6 months of referral. In January 2014, following initial demonstration of program feasibility, eligibility was expanded to *also include newly diagnosed individuals who had a CD4+ T-cell count <200/mm^3, active opportunistic infection, or an HIV seronegative sexual partner.* Importantly, the details of a patient's HIV testing history, symptoms and CD4 cell count were often not known at the time of referral. This resulted in several potentially eligible patients not receiving the intervention.

Intervention program participants and comparison groups included in analyses

We conducted two main comparative analyses to assess intervention impact: an intervention vs. no intervention analysis (looking at the same time period) and a pre- and post-intervention analysis (assessing change across multiple time periods). The first analysis considered all consecutive patients with new HIV infection who were referred to the clinic for care during the intervention period from July 2013 until December 31, 2014, and were either managed via the RAPID intervention program or not. The second (pre- and post-intervention) comparison also included data from an historical cohort of similar size who had been referred to SFGH in the pre-RAPID program period between 2006 and 2013. The historical cohort was selected using blocks of randomly assigned patient identification numbers from relevant periods. For all patient groups studied, analyses were limited to adult patients (≥18 years of age) initiating first outpatient HIV care at SFGH after a new diagnosis. Data from patients diagnosed for more than two years, patients transferring HIV care or already on ART at the time of referral were not included.

Data collection

Indicators of clinical care and treatment received, adverse events (including drug toxicities, immune reconstitution syndromes and treatment modifications), and virologic treatment outcomes were abstracted from electronic medical records through June 2015, allowing six months or more of follow-up after initial referral for all patients included in this study. Engagement in care was defined as having kept an appointment within the prior 6 months at

the time of dataset closure; loss-to-follow-up at this timepoint was defined as not being engaged in care and not having a documented transfer of care. Viral load and viral genotype data were only recorded as these were obtained clinically and available in the medical record. Genotyping involved sequencing of HIV reverse transcriptase and protease genes; HIV integrase sequencing was not routinely available at the time.

Statistical analysis

To assess whether the RAPID intervention impacted acceptability, safety, or short term efficacy of antiretroviral treatment, the primary analyses compared outcomes in the patients who were managed under the RAPID program protocol to those in patients referred to Ward 86 during the same time period but who were not managed under the RAPID program. Categorical characteristics were compared using Pearson's chi square or Fisher's Exact test where expected cell sizes were ≤5. Continuous variables were compared with a Student's t test. HIV-1 viral load (copies/mL) was log10 transformed for analyses. Data on time to first clinic visit, first primary care provider (PCP) visit, ART initiation, and viral suppression were complete through January 31, 2015 and were censored on that date (or, for patients known to have transferred care, on the date of the last available viral load test result). Data on ART safety and clinic appointment attendance were complete through June 1, 2015.

Time to viral suppression was defined as time from clinic referral to the first lab result with VL<200 copies/mL. Suppression was defined at this threshold [10] to allow for consistency across eras since the sensitivity of quantification assays changed over time. Median survival times with 95% confidence intervals were estimated using Kaplan-Meier estimators.

For the first main analysis, direct comparisons between RAPID program patients and the contemporaneous comparison group were made using the log rank test, and then followed up with Cox proportional hazards models, which allowed comparisons to be adjusted for integrase strand transfer inhibitor (INSTI)-based ART and baseline viral load. Because viral suppression could not be observed in patients who did not return to clinic at regular intervals, a competing risk regression model of time to viral suppression was conducted as an additional secondary analysis using the method of Fine and Gray [12]. For the competing risk regression, patients who were not observed to have VL<200 copies/mL by the time of their last available measurement and whose most recent viral load measurement was >6 months before the end of data collection in the initial phase of the study were considered to have the competing risk outcome.

The second (pre-and post-intervention) comparative analysis compared times to care milestones in the RAPID intervention cohort with similar data from a retrospective cohort of patients who were randomly sampled from the 2006–2009 "CD4-guided ART" era and the 2010–2013 "universal ART" era. This analysis paralleled the primary analysis and included graphing a Kaplan-Meier curve illustrating the proportions of patients achieving viral suppression over time from clinic referral in these three patient groups. Analyses were performed using Stata version 13.1. (Stata Corp., College Station, TX).

RESULTS

Patient characteristics

Among 86 outpatients referred for initiation of HIV care with newly diagnosed HIV infection, 39 were managed according to the RAPID intervention program and 47 received the clinic standard of care. None had private health insurance and only 8.1% reported previously having a primary care provider at the time they were referred. As shown in Table 1, most patients were male and of non-white race; patients frequently reported homelessness (27.9%), major mental health disorders (41.9%) and illicit substance use (41.9%). The demographic characteristics were similar between RAPID and non-RAPID groups. CD4+ T-cell count and viral load distributions were also similar for RAPID and non-RAPID patients. As expected, there was a substantially higher proportion of patients with acute or recent HIV infection in the RAPID group. In the RAPID group, 25.0% of patients with testing history documented were diagnosed with RNA positive/antibody-negative acute HIV infection and an additional 50.0% met had recent infection as defined by a prior negative HIV test within 6 months of their positive test date; in total 75.0% of the RAPID group therefore had acute or recent HIV infection. Document review also revealed 6.3% acute infections and 21.8% recent infections among the non-RAPID group (status that was not recognized at the time of referral).

Acceptance of RAPID ART

As shown in Figure 2,35 (89.7%) of 39 patients offered ART at their RAPID visit took the first dose in the clinic, and 37 (94.9%) had started ART within the first 24 hours following the visit. Differences in the achievement of key milestones of care among patient groups are shown in Table 2—times to each milestone are reported indexed either to the referral date (i.e., the date the clinic was contacted by the testing site) or to the date the diagnostic test sample was drawn. Referrals to RAPID occurred a median of 6 days (25–75th IQR: 2 to 11) after the HIV test, and typically occurred on the same day that HIV results were disclosed to the patient. Following referral, clinic intake and ART prescription both occurred a median of 1 day later for RAPID patients. Among non-RAPID patients, times to clinic intake and ART prescription were 10 and 22 days respectively ($p<0.001$).

Safety of RAPID ART

Most patients received INSTI-based ART, and the proportion receiving INSTI-based therapy was comparable between groups (RAPID patients, 89.7% vs. non-RAPID patients, 84.2%; $p=0.52$). The most common initial RAPID regimen was tenofovir disoproxil fumarate (TDF) plus emtricitabine plus dolutegravir, used in 66.7% of patients. ART regimen modifications were significantly more frequent among RAPID patients: in two RAPID cases ART was changed due to a rash, whereas in ten cases ART was changed for simplification (e.g. to an abacavir-lamivudine-dolutegravir single pill regimen) following receipt of the results of HLA B5701 testing. There were no ART modifications for virologic failure and no resistance-driven ART changes after genotype results became available.

Among 75 patients for whom resistance genotype information was available, transmitted drug resistance mutations were present in 26 (34.7%), with a major NNRTI mutations

present in 18 (24.0%) individuals (Table 2). Ability to obtain genotypes at follow-up visits was limited by rapid viral suppression. Integrase genotyping for INSTI resistance mutations was not available to clinicians during the evaluation period. We observed no cases in which major mutations were present to the prescribed ART regimen.

Engagement and retention in care

Transfer of care to another HIV clinic occurred in 8 (20.5%) of 39 patients in the RAPID group, and similarly, in 11 (23.4%) of 47 patients in the non-RAPID group. Loss to follow-up was also similar, occurring in 4 (10.3%) of 39 RAPID and 7 (14.9%) of 47 non-RAPID patients (p=0.52). No patients continuing in care at the clinic requested a change in their assigned provider.

Viral suppression

Data on time to viral suppression for RAPID and non-RAPID patient groups are shown in Table 2. Viral load measurements occurred with a median interest interval of 58 days (IQR: 47 to 83) and there were no differences between RAPID and concurrent non-RAPID groups (p=0.57). The median time to viral suppression (<200 copies/mL) in RAPID patients was 56 days from clinic referral, compared with 79 days among the non-intervention participants (p=0.009). Differences remained statistically significant when controlling for baseline viral load and integrase inhibitor use. When loss-to-follow-up was considered as a competing risk in sensitivity analyses, faster suppression in the RAPID group remained statistically significant. The second, pre- and post- intervention analysis compared RAPID ART initiation with ART initiation by primary providers under CD4-guided and universal ART recommendations in previous years. Figure 3 illustrates this Kaplan-Meier analysis. The median of 1.8 months from referral to viral suppression under RAPID contrasted with 4.3 months in the pre-RAPID, universal ART group, and 7.2 months in the CD4-guided ART group (p=0.0001).

DISCUSSION

In this study, we found that a health systems intervention to initiate antiretroviral therapy (ART) on the same day as HIV diagnosis was highly feasible in a real-world public health clinic in San Francisco. Same-day, observed initiation of antiretroviral treatment was well accepted, was well tolerated by patients, and did not appear to interfere with subsequent engagement in care. Among patients treated under recommendations for universal initiation of ART, receiving the intervention was further associated with a shorter duration of time to viral suppression: the time from referral to viral suppression was reduced from 4.3 months in non-intervention recipients to 1.8 months in those receiving the same-day ART intervention.

This intervention utilized a streamlined HIV treatment initiation model that is similar in important respects to models used in the treatment of other communicable diseases. We found that the use of same-day, observed dosing on the day of diagnosis, medication starter packs, and use of pre-approved regimens were all feasible for patients with newly-diagnosed HIV.

However, we also found that starting ART immediately required additional time from all members of our multidisciplinary team. Our new patients lacked health insurance and often had immediate housing, substance use or mental health treatment needs. The addition of same-day ART into the first clinic visit therefore increased the urgency of arranging health insurance and also compressed the time available for social workers to begin the process of psychological and social stabilization. Because ART was begun without some baseline laboratory results available, there were also intensified demands on clinical providers to consider early regimen modifications. While a RAPID approach is clearly feasible, additional work will be needed to demonstrate optimal systems for implementation in different practice settings.

There are several additional limitations to this non-randomized implementation study. First, because all subjects received a multi-component intervention, we were unable to determine which specific components (such as same-day appointments, or observed dosing) contributed to positive patient outcomes. It is therefore unclear whether programs that omit one or more of these elements could expect similar outcomes. Second, it is possible that faster virologic suppression rates among RAPID intervention recipients could be explained by unmeasured differences between the patients who were selected for the intervention and those who were not selected. However, the only differences evident between groups were higher baseline HIV viral load and more frequent acute and recent HIV infection in the intervention group—differences that are not expected to lead to faster rates of suppression.

However the fact that the intervention was feasible in the setting of acute and recent HIV infection is especially encouraging. An intensive RAPID approach may be particularly valuable in the setting of acute infection—during which immediate treatment can reduce HIV reservoir size [13,14] reduce complications [15] and eliminate acute phase transmission [16–20] which may drive urban epidemics [20].

In summary, these results provide evidence that prioritizing immediate ART initiation can reduce the time to achieving virologic suppression in newly diagnosed patients without negative consequences to the patient. A shorter time to viral suppression offers both clinical benefits to patients, but also prevention benefits to the community. More detailed studies are needed to examine the optimal design, overall impact and cost-effectiveness of scaled up strategies for RAPID ART initiation.

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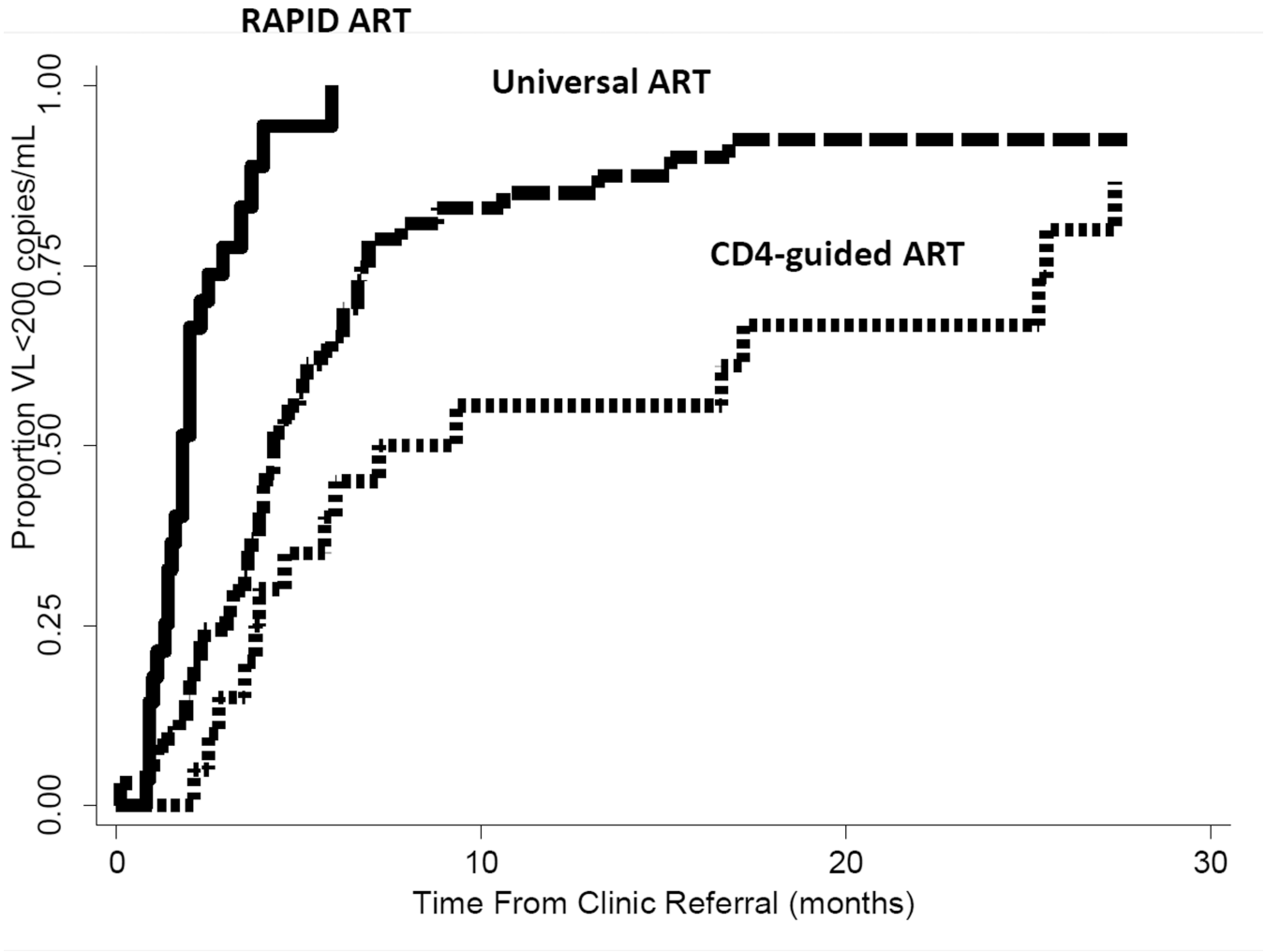

Figure 1. Standard of care and RAPID program models for initiation of outpatient antiretroviral therapy

In the RAPID model, a time-intensive "RAPID" visit was performed as soon as possible following a new diagnosis of HIV. ART was initiated by a RAPID program provider so that the first encounter with the assigned primary provider involved ART management. In the standard model ART was initiated by the primary provider after preparatory visits involving clinic intake, social, psychological, medical and laboratory evaluation.

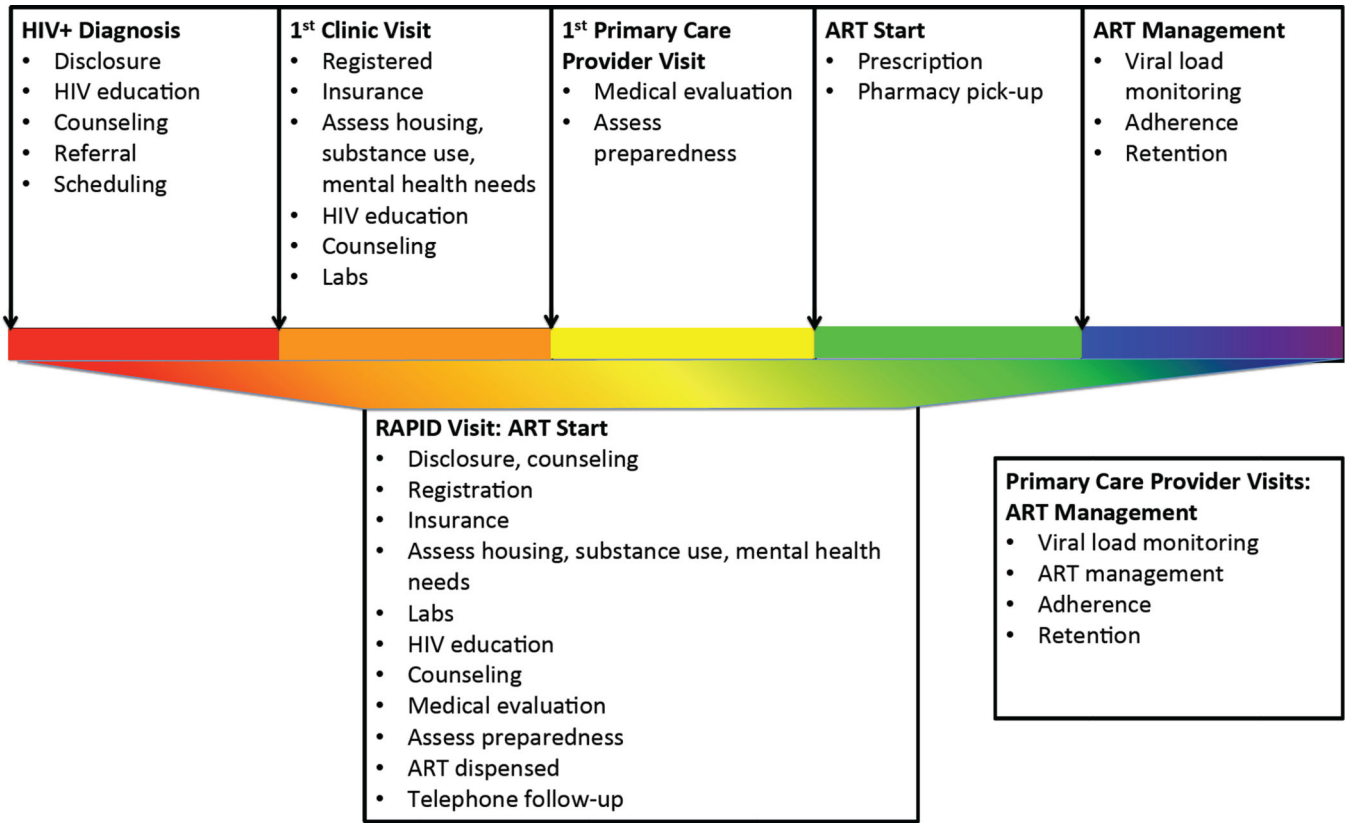

Figure 2. Uptake of ART when offered immediately after diagnosis

Data shown are for patients with a new HIV diagnosis and attending their first visit to the SFGH HIV Ciinic between 2013 and 2015 during the RAPID intervention program period. The percentage of patients choosing to take ART when offered by RAPID is shown by the black bars: ninety-five percent (37/39) patients elected to begin ART within a day of its being offered. Slower uptake among non-RAPID patients is related to the deferral of the offer to start ART.

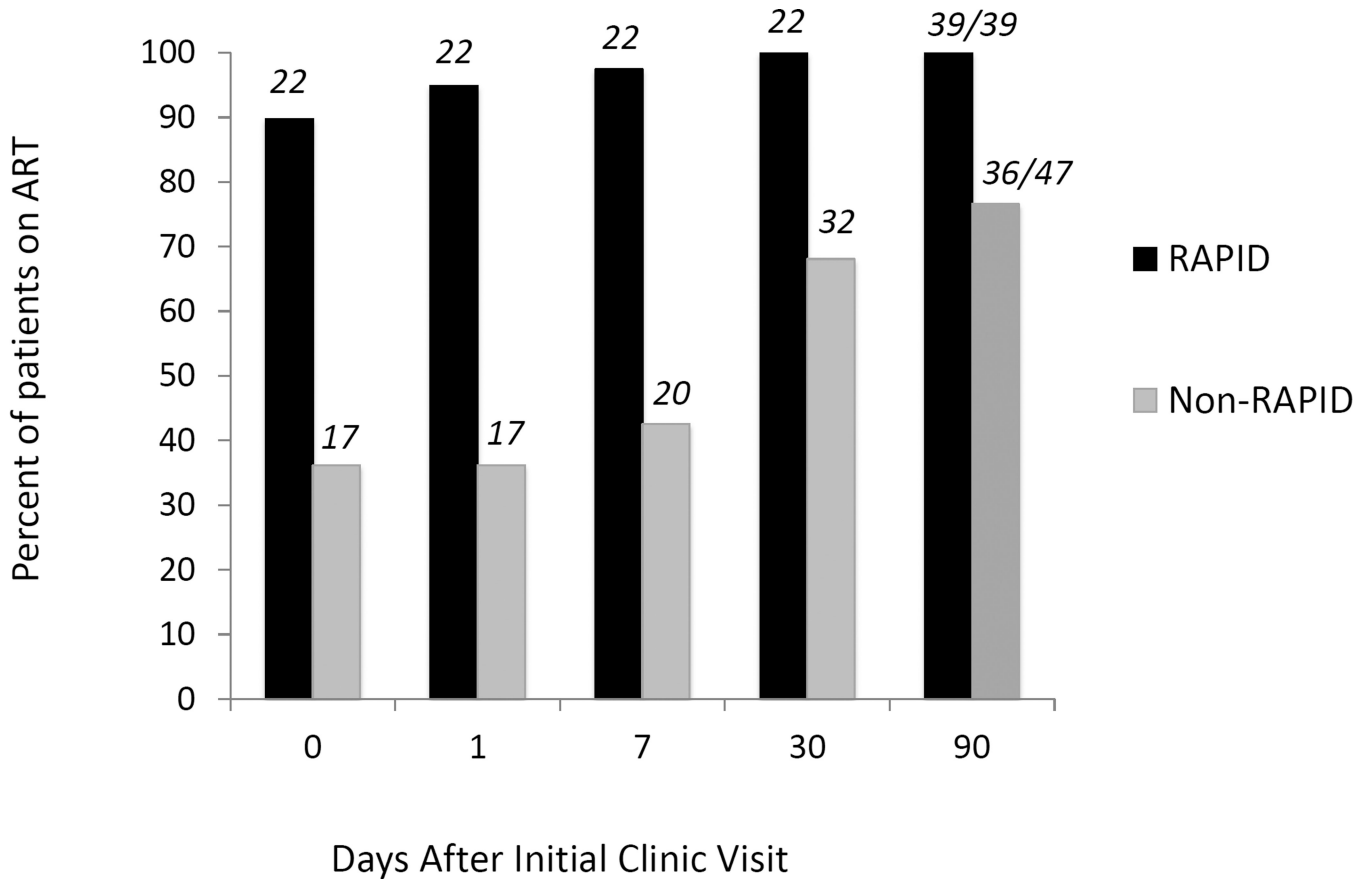

Figure 3. Time to viral suppression among patients newly diagnosed with HIV infection, by ART initiation strategy

This Kaplan-Meier plot shows the proportion of patients with viral load <200 copies/mL HIV RNA over time, following referral to the SFGH HIV clinic with a new diagnosis of HIV infection. Time to suppression for patients receiving the RAPID intervention in 2013–2015 (median 1.8 months) was significantly shorter than for patients treated under universal ART guidelines in the immediate pre-RAPID 2010–2013 period (4.3 months, p<.0001) and in the previous CD4 guided 2006–2009 period (7.2 months, p<.0001) represented by dotted line.

Table 1

Patient characteristics and ART use among 86 newly diagnosed patients referred to the San Francisco General Hospital HIV Clinic

Results are compared between 39 patients treated in the RAPID program for same-day, observed initiation of ART and 47 patients treated according to the clinic standard of care.

Characteristic	RAPID N=39	Non-RAPID N=47	p-value
Sociodemographic			
Age, mean (range)	31.6 (21 to 47)	34.8 (19 to 68)	0.14
Race/ethnicity, n (%)			0.034
Black	2 (5.1%)	12 (25.5%)	
Latino	18 (46.2%)	15 (31.9%)	
White	16 (41.0%)	13 (27.7%)	
Asian/Pacific Islander	3 (7.7%)	7 (14.9%)	
Sex, n (%)			0.11
Male	39 (100.0%)	44 (93.6%)	
Female	0 (0.0%)	3 (6.4%)	
Mental Health, n (%)			
Major disorder present	21 (53.9%)	15 (31.9%)	0.04
Housing, n (%)			0.97
Stably Housed	25 (64.1%)	31 (66.0%)	
Homeless	11 (28.2%)	13 (27.7%)	
Unknown	3 (7.7%)	3 (6.4%)	
Illicit Substance Use, n (%)			
Any reported	18 (46.2%)	18 (38.3%)	0.75
Clinical characteristics			
Baseline CD4 cell count[1], mean (range)	474 *(3 to 1391)*	417 *(11 to 1194)*	0.38
Baseline HIV RNA viral load[2], mean (range)	4.89 (*2.76 to 6.61)*	4.49 (*1.60 to 6.08)*	0.082
Acute or recent HIV Infection[3], n/N (%)			
Acute (RNA positive/Ab negative)	8/32 (*25.0%)*	2/32 (*6.3%)*	0.041
Recent (Ab negative within 6 months)	24/32 (*75.0%)*	9/32 (*28.1%)*	<0.001
Transmitted resistance			
Genotype obtained	32/39 (82.1%)	43/47 (91.5%)	0.21
Any[4]	8/32 (25.0%)	18/43 (41.9%)	0.13
Major NNRTI-R[4]	7/32 (21.9%)	11/43 (25.6%)	0.71
Major PI-R	1/32 (3.1%)	2/43 (4.7%)	0.99
Major NRTI-R	0 (0%)	1/43 (2.3%)	0.99
ART initiated[5,6]	39/39 (100%)	38/47 (80.9%)	0.003
INSTI use[6]	35/39[4] (89.7%)	32/38 (84.2%)	0.47
PI Use[6]	5/39 (12.8%)	5/38 (13.2%)	0.97
NNRTI use[6]	0/39 (0%)	3/38 (7.9%)	0.12

[1]Baseline CD4 T cell count units: cells/mm3

[2]Baseline HIV RNA Viral Load units: log10(copies/mL)

[3]Acute HIV infection status was defined by having a negative or indeterminate antibody test for HIV on the date of an initial positive test. Recent HIV infection status was defined by <6 months between diagnosis and prior negative HIV test result, which was known for only n=64/86 patients (74.4%) and among that overall group the proportion with acute or recent infection was 33/64 patients (51.8%). If known at the time of referral this was one indication for RAPID program enrollment.

[4]Presence of any RT or protease mutations consistent with transmitted drug resistance determined using current Stanford surveillance definitions. Major mutations conferring clinically significant resistance to given medications used current Stanfod clinical resistance definitions; there were 14 K103N, 3 V179D, and 1 V106A NNRTI mutations observed; only 2 major PI mutations (1 I54V, 1 L90M); and one virus with M184V. No K65R or T215F/Y mutations were observed and no 2 class resistant viruses were seen. Integrase resistance testing was not clinically available and was not performed.

[5]ART initiation documented at any time up to the time of maximum follow-up in June 2015 (at least six months after referral of the last patient included in the analysis).

[6]INSTI=integrase strand transfer inhibitor; PI=protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor. The most common regimen initiated in RAPID patients was truvada (tenofovir disoproxil fumarate/emtricitabine) plus dolutegravir (in 26 patients); others included stribild (tenofovir/emtricitabine/elvitegravir/cobicistat) in 7 patients; truvada plus darunavir plus ritonavir (4 patients); truvada plus raltegravir (1 patient) and triumeq (abacavir plus lamivudine plus dolutegravir) in 1 patient.

Table 2

Time to achievement of clinical milestones among newly diagnosed patients referred to the San Francisco General Hospital HIV Clinic

Outcomes are compared between patients who were offered the RAPID intervention and those who were not offered the intervention but who received an otherwise similar standard of care, either during the same time frame (the "non-RAPID" comparison group) or under evolving treatment guidelines during the years prior to the RAPID program.

Group	**RAPID**	**Non-RAPID**	**Universal ART era**	**CD4-guided era**	**Between-group comparisons**	
Referral years	2013–2014	2013–2014	2010–2013	2006–2009	RAPID vs. non-RAPID	RAPID vs. 2010–2013 Universal
Patients for whom ART recommended	All	All	All	CD4<500	(contemporaneous)	(pre-post intervention)
Received intervention	Yes	No	No	No		
N:	39	47	69	25	p-values[1]	
Time in days from referral to:						
Clinic intake visit	1 (0–5)	10 (7–17)	13 (7–26)	9 (2 – 44)	<0.001	<0.001
Primary provider visit	14 (3 –30)	26 (13 –105)	31 (17–60)	30 (7–65)	0.13	0.089
ART prescription	1 (0–7)	22 (14–48)	37 (26–148)	128 (39–520)	<0.001	<0.001
Viral suppression <200 cp/mL	56 (40–87)	79 (53–174)	132 (91–210)	218 (116–777)	0.009	<0.001
Time in days from diagnosis to:						
Referral to the clinic	6 (2–11)	11 (3–104)	14 (4–48)	33 (4–120)	0.004	0.008
Viral suppression <200 cp/mL	65 (52–119)	170 (79 – 363)	190 (113–302)	580 (138–971)	<0.001	<0.001

[1] P-values shown did not consider loss to follow-up as a competing risk (see text).