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BRIEF REPORT

Disparities in Integrase Inhibitor Usage in the Modern HIV Treatment Era: A Population-Based Study in a US City

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Integrase inhibitor–based (INSTI) antiretroviral therapy (ART) regimens are preferred for most people with HIV (PWH). We examined factors associated with INSTI use among PWH in San Francisco who started ART in 2009–2016. PWH who experienced homelessness were less likely, and older PWH were more likely, to use an INSTI.

Keywords. antiretroviral therapy; HIV; integrase strand transfer inhibitor; virologic suppression.

The recommended antiretroviral therapy (ART) for initial HIV treatment includes 1–2 nucleoside reverse transcriptase inhibitors (NRTIs) and an agent from a second antiretroviral class. Integrase strand transfer inhibitors (INSTIs) are now the dominant ART class used in combination with NRTI(s) for HIV treatment. By 2009, raltegravir, the first INSTI [1], received approval as initial therapy and was added to the Department of Health and Human Services (DHHS) guidelines as a preferred regimen when starting HIV treatment [2]. By 2014, INSTI-based regimens outnumbered other ART classes in the DHHS guidelines' preferred regimens, and by 2017 INSTI-based regimens were the only preferred regimens [2]. INSTIs are well tolerated, and second-generation INSTIs, such as dolutegravir and bictegravir, have a high genetic barrier to resistance, both as first-line regimens [3] and in switch studies [4], as well as in salvage regimens [5]. Given the tolerability, potency, and high barrier to resistance of INSTIs, the World Health Organization has recommended that countries worldwide transition to tenofovir disoproxil fumarate-lamivudine-dolutegravir (TLD), an INSTI-based regimen, as first-line therapy [6]. In a US study of >30 000 individuals, INSTI use was associated with greater odds of undetectable viral load [7].

The goal of this analysis was to understand factors associated with access to INSTI-based regimens among people with HIV (PWH) who initiated ART from 2009 to 2016 in San Francisco (SF). Despite improving therapeutic options for HIV treatment, disparities in viral suppression and mortality remain in the United States, particularly for PWH who experience homelessness [8–10]. We hypothesized that homeless PWH would have lower rates of INSTI-based regimen prescription compared with housed PWH. Given the tolerability advantages and high potency, INSTIs have the potential to benefit populations that have lower virologic suppression rates.

METHODS

All SF residents who reported to the SF Department of Public Health (SFDPH) HIV surveillance case registry with evidence of ART initiation from 2009 to 2016 were included, which we estimate includes 99% of PWH attending SF care sites [10]. The procedures followed in this study were in accordance with the ethical standards of the Helsinki Declaration. A regimen was designated as INSTI-containing if an INSTI was a component of the ART regimen. A suppressed viral load was defined as <200 copies/mL. Patient characteristics were collected at the time of HIV diagnosis through mandatory reporting, through medical chart review, and/or were provided by the diagnosing provider. Collection of antiretroviral regimen and laboratory data continued through November 30, 2019. Chi-square tests were used to examine bivariate characteristics associated with INSTI initiation. Cox proportional hazards models were then used to analyze characteristics associated with the rate of ever being prescribed an INSTI. Analyses were adjusted for demographics, transmission group, insurance status, housing status, and treatment initiation year. The latest HIV viral load result (categorized as unsuppressed or suppressed) occurring in the 6 months before the first INSTI prescription was also included to adjust for greater virologic failure among key populations (such as homeless PWH), potentially leading to greater ART switching. Participants were censored if ART data were no longer available due to moving out of San Francisco's jurisdiction, being lost to follow-up, or if they died.

RESULTS

Overall, 3255 PWH were first prescribed ART from 2009 through 2016 in SF. Of these, 31% were age <30 years and 14% were age 50+ years, 38% initiated ART with an INSTI-based

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regimen, and 13% had experienced homelessness. Several populations were less likely to have been started on an INSTI-based regimen: homeless vs not known to be homeless PWH (31% vs 39%; $P = .01$), people who inject drugs (PWID; 30%) vs men who have sex with men transmission groups (40%; $P < .001$), and persons with public (35%) or no insurance (34%) vs private insurance at diagnosis (42%; $P < .001$). For the remaining 2028 PWH who did not initiate an INSTI, 46% eventually switched to an INSTI-containing regimen. Overall, the percentage of PWH who ever received an INSTI increased over time, with 49% in 2009 ever receiving an INSTI, rising to 60%, 57%, 59%, 70%, 85%, 88%, and 93% in 2010, 2011, 2012, 2013, 2014, 2015, and 2016, respectively ($P < .001$). In the multivariable analysis, homeless vs housed PWH had a lower rate of INSTI use (adjusted hazard ratio [AHR], 0.84; 95% CI, 0.73–0.98) (Table 1). Older vs younger PWH (age 50+ vs age <30; AHR, 1.16; 95% CI, 1.01–1.34) and those initiating ART in later years ($P_{trend} < .001$) had a higher rate of INSTI usage.

DISCUSSION

For SF residents with HIV who initiated ART from 2009 through 2016 and who were followed through November 2019, INSTI use rose dramatically, with nearly 90% of those initiating ART in 2016 being prescribed an INSTI. Characteristics such as high tolerability and high barrier to resistance of second-generation INSTIs have led to INSTIs being placed as first-line therapy on national and international guidelines [1–5]. Despite these potential benefits, homeless PWH were less likely to initiate or ever switch to an INSTI regimen, even after controlling for ART initiation year.

Given that PWH experiencing homelessness have greater adherence challenges, lower virologic suppression, and higher mortality [8–10], it is important to ensure that they have access to the most efficacious ART, in addition to offering housing assistance and other psychosocial services. There are several possible explanations for why homeless PWH had a lower rate of INSTI regimen prescription. Anticipated adherence challenges [8, 9], greater clinical experience with other antiretroviral classes, particularly in earlier years, lower retention in care [11], or competing priorities [12] may underlie the decision of clinicians to defer switching to INSTIs among these populations. Conversely, clinicians may offer INSTIs at a higher rate to older individuals due to perceived greater adherence and reliability in returning for timely follow-up. In 2019, SF homeless PWH were less likely to receive viral load or CD4+ cell count monitoring (56% vs 82%) in spite of lower virologic suppression rates, likely reflecting lower retention in care [11]. Clinicians may defer ART switch due to concerns that PWH in these key populations may not return for laboratory monitoring following switch or due to the need to address other pressing health issues. In addition, concerns about future development of resistance could have led the practitioner to favor protease inhibitor (PI)–based regimens if there were anticipated adherence challenges, given that failure on PIs is less likely to lead to resistance [5]. However, for initial therapy, failure on second-generation INSTI-based regimens

Table 1. Factors Associated With Rate of INSTI-Based ART Use Among 3255 San Francisco Residents who Were Diagnosed With HIV 2009–2016

Factor	Adjusted HR	95% CI	*P* Value
Female vs male sex[a]	1.01	0.81–1.27	.91
Race/ethnicity vs White			
Black	0.95	0.84–1.09	.49
Latinx	0.95	0.85–1.06	.33
Other	0.91	0.80–1.04	.18
Transmission group vs MSM			
PWID	0.85	0.70–1.05	.13
MSM/PWID	0.93	0.81–1.05	.22
Other	0.97	0.8–1.21	.79
Age vs age <30 y			
Age 30–39 y	1.11	0.98–1.26	.09
Age 40–49 y	1.13	1.00–1.29	.05
Age 50+ y	1.15	1.01–1.34	.03
Insurance status vs private insurance			
Public vs private insurance	0.93	0.82–1.04	.20
No insurance vs private	0.90	0.80–1.00	.06
Homeless housing status	0.84	0.73–0.98	.02
ART initiation year vs 2009–2010			
2011–2012	1.47	1.30–1.67	<.001
2013–2014	2.67	2.34–3.06	<.001
2015–2016	3.46	3.00–4.01	<.001

Abbreviations: ART, antiretroviral therapy; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PWID, people who inject drugs.

[a]Analyses also adjusted for the latest unsuppressed vs suppressed viral load occurring in the 6 months before INSTI prescription, analyzed as a time-dependent covariate.

leading to INSTI resistance is rare. In the FLAMINGO study, dolutegravir-based initial regimens were superior to regimens based on darunavir, the most commonly used PI in the United States, and no treatment-emergent resistance mutations occurred in either group [3]. When selecting ART regimens for patients, concerns about adherence should be weighed against the potential for higher virologic efficacy, particularly in populations with lower virologic suppression rates such as homeless PWH. Furthermore, given that clinicians are generally poor at predicting the adherence of their patients [13], clinicians should initiate patients on the most efficacious regimen, consistent with their patient's preferences, through shared decision-making.

Differences in INSTI ART initiation by insurance status did not persist in adjusted analysis examining INSTI use over time. Given that all uninsured SF residents are eligible for a municipal health access program called *Healthy San Francisco* and supplemental medication coverage is available through the *US AIDS Drug Assistance Program*, non–privately insured PWH were unlikely to have experienced cost differences with INSTI use, although perceived cost, insurance churn, and burdensome bureaucratic requirements could still interfere with INSTI prescription and ART access. Public health authorities should ensure that patients have continuous access to the most efficacious ART regimens, regardless of insurance status. PWID were less likely to initiate INSTIs, although there were no differences in INSTI usage over time in adjusted analysis controlling for other factors such as homelessness and ART initiation year. Decreased INSTI use among PWID may be mediated by other factors, such as homelessness and/or declines in HIV diagnoses among PWID in later years [11], when INSTI use is more common.

There are several limitations to this analysis. Results from SF PWH, the majority of whom are male, may not be representative of other populations and jurisdictions. We also cannot exclude the possibility that some participants went on to initiate an INSTI-based regimen after leaving the SF jurisdiction—time periods after a participant left SF were censored in our analysis. There are also a small number of care sites that do not allow the SFDPH to access ART history and medical records; however, these are estimated to impact <1% of all PWH in San Francisco [10]. Finally, we were not able to differentiate switching to an INSTI because of antiretroviral resistance, simplification, tolerability, or other concerns because comprehensive data regarding reasons for changes in regimen were not available.

In conclusion, INSTI-based regimen use, both as first-line and subsequent HIV therapy, has dramatically risen over time. Despite the potential benefits of INSTI-based regimens for efficacy in achieving virologic suppression, populations with higher rates of virologic nonsuppression, such as PWH experiencing homelessness [7–10], were less likely to use an INSTI-based regimen over time. Providers should engage in shared decision-making with their patients when selecting ART regimens, and health systems should support access to the most potent ART regimens.

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Patient consent. The SFDPH HIV surveillance unit approved this work. The SFDPH did not require informed consent to be obtained from participants as only review of surveillance records was performed.

References

1. Steigbigel RT, Cooper DA, Teppler H, et al. Long-term efficacy and safety of raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. Clin Infect Dis **2010**; 50:605–12.
2. Madhav N, Oppenheim B, Gallivan M, et al. Pandemics: risks, impacts, and mitigation. In: Jamison DT, Gelband H, Horton S, et al, eds. Disease Control Priorities: Improving Health and Reducing Poverty. 3rd ed. Washington, DC: The International Bank for Reconstruction and Development/The World Bank; **2017**.
3. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV **2015**; 2:e127–36.
4. Trottier B, Lake JE, Logue K, et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, phase IIIb study. Antivir Ther **2017**; 22:295–305.
5. Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. Lancet Infect Dis **2019**; 19:253–64.
6. Spreeuwenberg P, Kroneman M, Paget J. Reassessing the global mortality burden of the 1918 influenza pandemic. Am J Epidemiol **2018**; 187:2561–7.
7. Nance RM, Delaney JAC, Simoni JM, et al. HIV viral suppression trends over time among HIV-infected patients receiving care in the United States, 1997 to 2015: a cohort study. Ann Intern Med **2018**; 169:376–84.
8. Clemenzi-Allen A, Geng E, Christopoulos K, et al. Degree of housing instability shows independent "dose-response" with virologic suppression rates among people living with human immunodeficiency virus. Open Forum Infect Dis **2018**; 5:XXX–XX.
9. Spinelli MA, Hickey MD, Glidden DV, et al. Viral suppression rates in a safety-net HIV clinic in San Francisco destabilized during COVID-19. AIDS. **2020**; 34:2328–31. doi: 10.1097/QAD.0000000000002677.
10. Spinelli MA, Hessol NA, Schwarcz S, et al. Homelessness at diagnosis is associated with death among people with HIV in a population-based study of a US city. AIDS **2019**; 33:1789–94.
11. Enanoria W, Scheer S, Hsu L, Buckman A. *San Francisco HIV Epidemiology Annual Report 2019*. San Francisco: San Francisco Department of Public Health HIV Epidemiology Section; **2020**.
12. Clemenzi-Allen AA, Hartogensis W, Cohen SE, Gandhi M, Geng E, Christopoulos K. Evaluating the impact of housing status on gonorrhea and chlamydia screening in an HIV primary care setting. Sex Transm Dis **2019**; 46:153–8.
13. Phillips LA, Leventhal EA, Leventhal H. Factors associated with the accuracy of physicians' predictions of patient adherence. Patient Educ Couns **2011**; 85:461–7.