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A) Baseline Characteristics at INSTI start

Table S1. ART regimen category prior to INSTI start, for ART experienced persons

Variable n(%) unless otherwise specified	Raltegravir ***N*=481**	Elvitegravir-cobicistat ***N*=312**	Dolutegravir ***N*=455**	TOTAL **N=1248**
Prior ART regimen				
PI + 2 NtRTI	231 (48.0))	133 (42.6)	188 (41.3)	552 (44.2)
NNRTI + 2 NtRTI	140 (29.1)	112 (35.9)	110 (24.2)	362 (29.0)
INSTI + 2 NtRTI	9 (1.9)	25 (8.0)	82 (18.0)	116 (9.3)
Other ARV combination with INSTI	0	21 (6.7)	50 (11.0)	71 (5.7)
Other ARV combination without INSTI	101 (21.0)	21 (6.7)	25 (5.5)	147 (11.8)

ART, antiretroviral therapy; ARV, antiretroviral; INSTI, integrase strand transfer inhibitor; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NtRTI, Nucleoside(-tide) reverse transcriptase inhibitor; PI, Protease inhibitor.

Table S2. Initial INSTI dose

INSTI dose at time of first prescription		**Reason for higher INSTI dose**	
	n (% of N)	**Drug interaction**	**INSTI resistance**
Raltegravir	**N=551**		
400 mg twice daily (standard)	548 (99.5)	na	na
800 mg twice daily	3 (0.5)	3[a]	
Elvitegravir	**N= 394**		
150 mg once daily (standard)	394 (100)	na	na
Dolutegravir	**N= 519**		
50 mg once daily (standard)	503 (96.9)	na	na
50 mg twice daily	16 (3.1)	11[a]	5

INSTI, integrase strand transfer inhibitor; na, not applicable;

[a]3/3 raltegravir and 10/11 dolutegravir-treated persons who received a high, initial INSTI dose due to a drug interaction had a subsequent reduction to standard INSTI dose within 1-12 months, following removal of the interacting drug.

Table S3. Details of Other[a] ARV combinations at the time of initial INSTI prescription

Concurrent ARVs in persons with Other[a] ARV combination, n(%)	Raltegravir N= 226	Elvitegravir-cobicistat N= 43	Dolutegravir N= 85	Total N=354
	By ARV component			
NNRTI (any)	***95 (42.0)***	***1 (2.3)***	***7 (8.2)***	***103 (29.1)***
Nevirapine	15 (6.6)	0	0	15 (4.2)
Efavirenz	8 (3.5)	0	0	8 (2.3)
Etravirine	70 (31)	1 (2.3)	6 (7.1)	77 (21.8)
Rilpivirine	3 (1.3)	0	1 (1.2)	4 (1.1)
PI (any)	***179 (79.2)***	***35 (81.4)***	***74 (87.1)***	***288 (81.4)***
Lopinavir	20 (8.9)	0	2 (2.4)	22 (6.2)
Atazanavir	43 (19.0)	23 (53.5)	20 (23.5)	86 (24.3)
Darunavir	115 (50.9)	12 (27.9)	52 (61.2)	179(5.6)
Saquinavir	1 (0.44)	0	0	1 (0.3)
Ritonavir (booster)	175 (77.4)	0	72 (84.7)	247 (69.8)
NtRTI (any)	***220 (97.3)***	***43 (100)***	***82 (96.5)***	***345 (97.5)***
Lamivudine or Emtricitabine	156 (69.0)	43 (100)	72 (84.7)	271 (76.6)
Abacavir	54 (23.9)	7 (16.3)	32 (37.7)	93 (26.3)
Tenofovir disoproxil fumarate	68 (30.1)	43 (100)	42 (49.4)	153 (43.2)
Zidovudine	8 (3.5)	0	0	8 (2.3)
Stavudine	1 (0.44)	0	2 (2.4)	3 (0.8)
Other (any)	***14 (6.2)***	***0***	***6 (7.1)***	***20 (5.6)***
Maraviroc	13 (5.8)	0	5 (5.9)	18 (5.1)
Enfuvirtide	1 (0.44)	0	1 (1.2)	2 (0.6)
	By ARV combination			
2 ARV classes	***13 (5.8)***	***7 (16.3)***	***9 (10.6)***	***29 (8.2)***
NtRTI[a]/ INSTI	7 (3.1)	7 (16.3)	6 (7.1)	20 (5.6)
PI-b/ INSTI	6 (2.7)	0	3 (3.5)	9 (2.5)
3 ARV classes	***195 (86.3)***	***36 (83.7)***	***73 (85.9)***	***304 (85.9)***
NtRTI/ PI-b/ INSTI	104 (46.0)	35 (81.4)	63 (74.1)	202 (57.1)
NtRTI/ PI/ INSTI	3 (1.3)	0	1 (1.2)	4 (1.1)
NtRTI/ NNRTI/ INSTI	32 (14.2)	1 (2.3)	2 (2.4)	35 (9.9)
PI-b/ NNRTI/ INSTI	48 (21.2)	0	2 (2.4)	50 (14.1)
Other, includes Maraviroc	8 (3.5)	0	5 (5.9)	13 (3.7)
4 or 5 ARV classes	***18 (8.0)***	***0***	***3 (3.5)***	***21 (5.9)***
NtRTI/ PI-b/ NNRTI/ INSTI	12 (5.3)	0	2 (2.4)	14 (4.0)
Other, includes Maraviroc or Enfuvirtide	6 (2.7)	0	1 (1.2)	7 (2.0)

[a]Other ARV combination, ARVs co-prescribed with the INSTI in a combination other than abacavir-lamivudine or tenofovir disoproxil fumarate- emtricitabine/ lamivudine.

INSTI, Integrase strand transfer inhibitor ; NtRTI Nucleoside(-tide) Reverse Transcriptase Inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; PI; Protease Inhibitor; PI-b, Protease Inhibitor with pharmacokinetic booster (cobicistat or ritonavir).

B) Outcome Data

Table S4. Changes to ARVs concurrently prescribed with INSTI during the 2 year follow-up

Changes to co-prescribed ARVs during follow-up, n(%)	Raltegravir N=57	Elvitegravir-cobicistat N=7	Dolutegravir N=66	Total N=130
NtRTI change- any	***28 (49.1)***	***0***	***44 (65.7)***	***71 (54.6)***
Switch Abacavir to Tenofovir DF	4 (7.0)	0	6 (9.0)	10 (7.7)
Switch Tenofovir DF to Abacavir	20 (35.1)	0	33 (49.3)	53 (40.8)
Other NtRTI change	4 (7.0)	0	4 (6.0)	8 (6.2)
PI change- any	***19 (33.3)***	***7 (100)***	***17 (25.4)***	***43 (33.1)***
Switch PI	9 (15.8)	1 (14.3)	6 (9.0)	16 (12.3)
Discontinue PI	5 (8.8)	3 (42.9)	7 (10.4)	15 (11.5)
Add PI	5 (8.8)	3 (42.9)	4 (6.0)	12 (9.2)
NNRTI change- any	***4 (7.0)***	***0***	***2 (3.0)***	***6 (4.6)***
Switch NNRTI	2 (3.5)	0	0	2 (1.5)
Discontinue NNRTI	0	0	2 (3.0)	2 (1.5)
Add NNRTI	2 (3.5)	0	0	2 (1.5)
Other ARV change	***6 (10.5)***	***0***	***4 (6.0)***	***10 (7.7)***

NtRTI Nucleoside(-tide) Reverse Transcriptase Inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; PI; Protease Inhibitor; Tenofovir DF, tenofovir disoproxil fumarate

Table S5. Other reason for physician-ordered INSTI discontinuation

Reason for INSTI discontinuation n (%)	Raltegravir N= 144	Elvitegravir-cobicistat N= 57	Dolutegravir N=36	p-value
Treatment failure/ Drug resistance	15 (10.4)	8 (14)	6 (16.7)	0.529
Adverse drug reaction (to other ARV)[a]	7 (4.9)	10 (17.5)	4 (11.1)	0.015
Drug interaction	4 (2.8)	15 (26.3)	1 (2.8)	<0.001
ART simplification	84 (58.3)	5 (8.8)	8 (22.2)	<0.001
Other/Unspecified reason	42 (29.2)	21 (36.8)	19 (52.8)	0.027

ARV, antiretroviral drug; ART, antiretroviral therapy;

[a]Suspected adverse drug reaction to an ARV other than the INSTI

Table S6-a. INSTI Adverse Drug Reaction symptom detail

Symptom Class n (% of total N treated)	Raltegravir N = 551	Elvitegravir-cobicistat N = 394	Dolutegravir N = 519	p-value
Any ADR	***24 (4.6)***	***38 (9.6)***	***27 (5.20)***	***0.002***
Central Nervous System (CNS)	*9 (1.6)*	*11 (2.8)*	*18 (3.5)*	*0.162*
Headache	4 (0.7)	2 (0.5)	3 (0.6)	
Insomnia/sleep disorder	4 (0.7)	3 (0.8)	7 (1.4)	
Nightmare/vivid dreams	2 (0.4)	1 (0.3)	2 (0.4)	
Vertigo/dizziness	1 (0.2)	0	1 (0.2)	
Tremor	1 (0.2)	0	0	
Altered mental status	0	1 (0.3)	3 (0.6)	
Altered mood	0	5 (1.3)	4 (0.8)	
Unspecified CNS	1 (0.2)	2 (0.5)	1 (0.2)	
Fatigue/malaise/low energy	*0*	*5 (1.3)*	*3 (0.6)*	*0.019*
Gastrointestinal (GI)	*13 (2.4)*	*21 (5.3)*	*10 (1.9)*	*0.006*
Nausea and/or vomiting	7 (1.3)	5 (1.3)	5 (1.0)	
Diarrhea	2 (0.4)	7 (1.78)	5 (1.0)	
Loss of appetite	0	1 (0.3)	0	
Reflux	0	1 (0.3)	0	
Gas (flatulence, belching)	0	2 (0.5)	0	
GI discomfort/pain	1 (0.2)	0	2 (0.4)	
GI upset, unspecified	5 (0.9)	6 (1.52)	1 (0.2)	
Hepatic	*0*	*2 (0.5)*	2 (0.4)	*0.200*
Elevated hepatic transaminases	0	2 (0.5)	2 (0.4)	
Skin	*3 (0.5)*	*1 (0.3)*	1 (0.2)	*0.643*
Rash/hives	3 (0.5)	1 (0.3)	1 (0.2)	
Other	*2 (0.4)*	*6 (1.5)*	2 (0.4)	*0.080*
Night sweats	0	1 (0.3)	0	
Weight loss	0	1 (0.3)	0	
Weight gain	0	1 (0.3)	1 (0.2)	
Lipodystrophy	0	1 (0.3)	0	
Pain (general)	0	1 (0.3)	0	
Myalgia	1 (0.2)	0	1 (0.2)	
Arthralgia	1 (0.2)	0	0	
Renal effects	0	2 (0.5)	0	

ADR, adverse drug reaction attributed to the INSTI; INSTI, Integrase strand transfer inhibitor; Any ADR counts one symptom per person for each INSTI; Symptom category totals count one symptom per symptom category per person for each INSTI. P-value compares category totals across INSTI categories, calculated by Pearson's chi-square or Fisher's Exact test.

Table S6-b. INSTI Adverse Drug Reactions classified as severe[a] by the reporter

Symptom Class	ADR reports (n severe/N total %)		
	Raltegravir	Elvitegravir-cobicistat	Dolutegravir
	N = 24	N = 38	N = 27
Any ADR with severe[a] symptoms	***4 (16.7)***	***4 (10.5)***	***3 (11.1)***
Central Nervous System (CNS)			
Headache	1		
Insomnia/sleep disorder			1
Gastrointestinal (GI)			
Nausea and/or vomiting	2	1	1
Diarrhea		1	
Hepatic			
Elevated hepatic transaminases 5-10x upper limit of normal		1	1
Skin			
Rash/hives	1		
Other			
Acute renal insufficiency		1	

[a]Symptom severity was designated by the clinician reporter, and was not specified for the majority (70%) of ADRs. Eleven of 89 (12%) ADRs were designated "severe" by the reporter. No cases were described as potentially life-threatening.

Table S7. Bivariate analyses: INSTI ADR rates stratified by baseline variables

Baseline Variables at INSTI initiation	Total category N	ADR frequency n (n/N%)	Crude ADR rate /100 person-yr (95% CI)	p value
INSTI				
Raltegravir	551	24 (4.4%)	2.91 (1.95, 4.35)	**0.006**
Elvitegravir-cobicistat	394	38 (9.6%)	5.94 (4.32, 8.16)	
Dolutegravir	519	27 (5.2%)	2.96 (2.03, 4.31)	
Age				
<40 yr	380	26 (6.8%)	4.24 (2.89, 6.23)	0.465
≥40 yr	1084	63 (5.8%)	3.57 (2.79, 4.57)	
Sex				
Female	305	24 (7.9%)	5.06 (3.39, 7.55)	0.111
Male	1159	65 (5.6%)	3.42 (2.68, 4.36)	
Pre-INSTI pVL < 50 copies/mL				
No	627	36 (5.7%)	3.75 (2.71, 5.2)	0.991
Yes	837	53 (6.3%)	3.74 (2.86, 4.9)	
Pre-INSTI CD4 ≥ 200 µL/mL				
No	240	16 (6.7%)	4.83 (2.96, 7.88)	0.289
Yes	1224	73 (6%)	3.57 (2.84, 4.49)	
Hepatitis C antibody positive				
No/Unknown	929	53 (5.7%)	3.39 (2.59, 4.44)	0.222
Yes	535	36 (6.7%)	4.42 (3.19, 6.13)	
INSTI start year				
Period 1: Jan 2012- Apr 2013	280	10 (3.6%)	2.23 (1.20, 4.15)	0.065
Period 2: May 2013- Dec 2013	275	22 (8.0%)	5.26 (3.46, 7.99)	
Period 3: Jan 2014- Dec 2014	909	57 (6.3%)	3.77 (2.91, 4.89)	
Prior ART history				
ART naive	216	10 (4.6%)	2.91 (1.57, 5.41)	0.068
ART experienced but INSTI naive	1028	58 (5.6%)	3.43 (2.66, 4.44)	
ART and INSTI experienced	220	21 (9.5%)	6.09 (3.97, 9.34)	
Time on ART in years				
<5 years (where tx naive= 0)	667	40 (6%)	3.76 (2.76, 5.12)	0.867
≥5 years	716	45 (6.3%)	3.83 (2.86, 5.13)	
Missing	81	4 (4.9%)	2.93 (1.1, 7.8)	
ARV co-prescribed with INSTI				
tenofovir DF+ 3TC/FTC	674	48 (7.1%)	4.44 (3.35, 5.9)	0.233
abacavir+3TC	436	25 (5.7%)	3.42 (2.31, 5.05)	
Other ARV combination	354	16 (4.5%)	2.83 (1.74, 4.63)	
PI co-prescribed with INSTI				
Regimen does not include PI	1176	75 (6.4%)	3.91 (3.12, 4.91)	0.372
Regimen includes PI	288	14 (4.9%)	3.04 (1.80, 5.13)	

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Table S7. continued

Baseline Variables at INSTI initiation	Total category N	ADR frequency n (n/N%)	Crude ADR rate /100 person-yr (95% CI)	p value
≥1 other new ARV in the ART regimen				
No	812	48 (5.9%)	3.58 (2.7, 4.75)	0.643
Yes, or initial ART regimen	652	41 (6.3%)	3.95 (2.91, 5.37)	
Previous report of any ARV ADR				
No, or ART naive	664	30 (4.5%)	2.82 (1.97, 4.03)	**0.033**
Yes	800	59 (7.4%)	4.5 (3.49, 5.81)	
Previous report of INSTI ADR				
No, or ART naive	1435	86 (6%)	3.69 (2.99, 4.56)	0.402
Yes	29	3 (10.3%)	6.29 (2.03, 19.5)	
Reason for switching to the INSTI (may include more than one reason per person)				
Treatment failure/ drug resistance				
failure	81	4 (4.9%)	2.86 (1.07, 7.62)	0.562
not failure, or ART naive	1383	85 (6.2%)	3.8 (3.07, 4.7)	
Adverse Drug reaction				
ADR	546	37 (6.8%)	4 (2.9, 5.53)	0.603
Not ADR, or ART naive	918	52 (5.7%)	3.58 (2.73, 4.7)	
Drug interaction				
Drug interaction	167	6 (3.6%)	2.26 (1.02, 5.04)	0.157
Not drug interaction, or ART naive	1297	83 (6.4%)	3.93 (3.17, 4.87)	
Simplification				
Simplification	323	23 (7.1%)	4.16 (2.76, 6.26)	0.571
not simplification, or ART naive	1141	66 (5.8%)	3.62 (2.84, 4.61)	

ADR, adverse drug reaction attributed to the INSTI; ARV, antiretroviral; ART, antiretroviral therapy; INSTI, Integrase strand transfer inhibitor; FTC, emtricitabine; 3TC, lamivudine; PI, protease inhibitor.
P-value compares category totals across INSTI categories, Crude ADR rate and p-value calculated by Poisson regression.
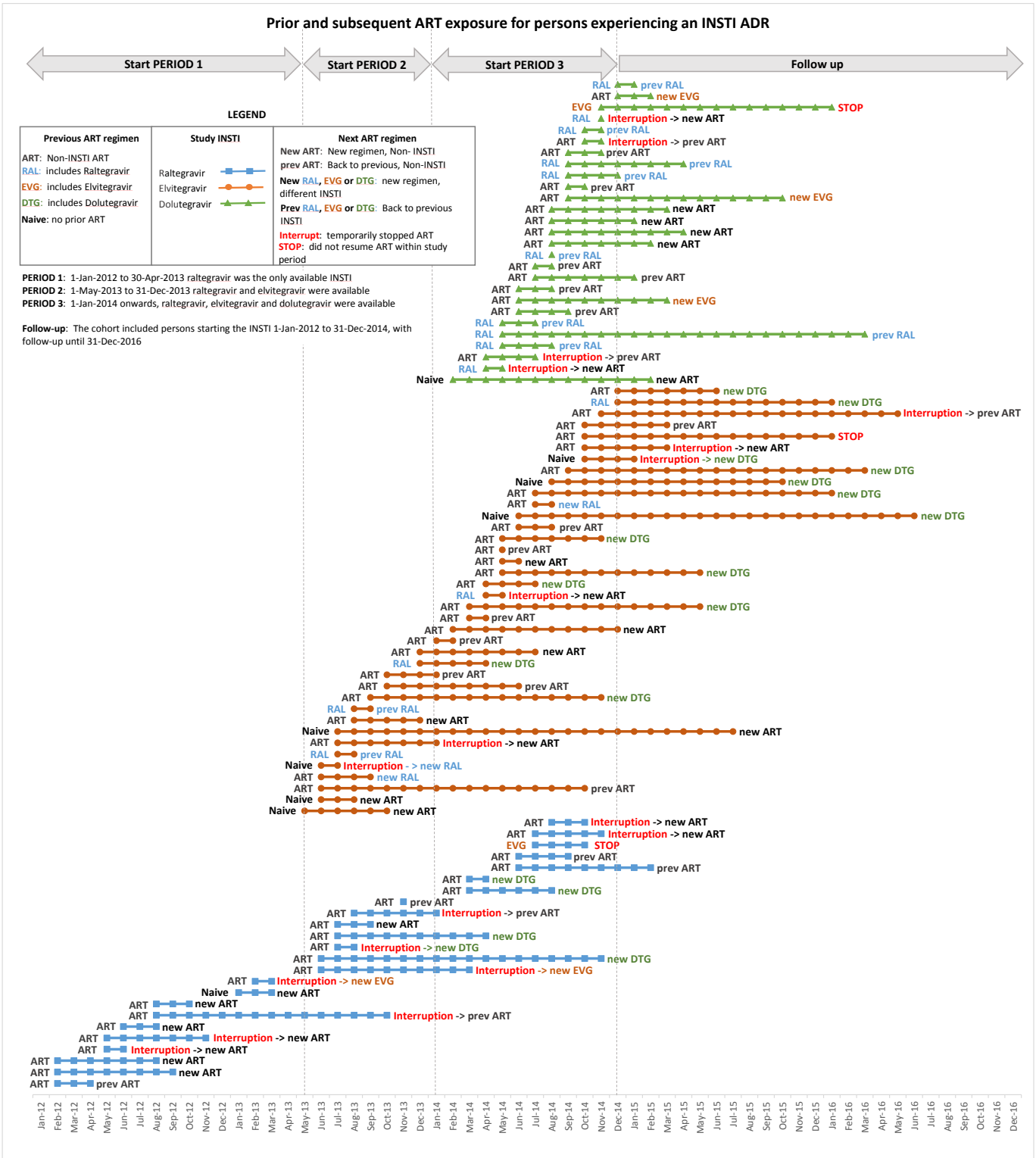
Figure S1. INSTI exposure timeline for persons with INSTI Adverse Drug Reaction