Supplementary Content

Note: in this article, we use standard abbreviations for antiretroviral agents as defined in the DHHS Guidelines for the Use of Antiretroviral Agents for Adults and Adolescents Living with HIV[1]

Further algorithm details (additional comments at https://www.hivassist.com/about/methodology)

We constructed decision rules to guide antiretroviral (ARV) selection based on literature, guidelines, and clinical experience that were incorporated into the multi-attribute function for multi-drug ARV evaluation. A composite utility weight for each ARV individually was first generated by considering the impact of comorbidities, comedications, side-effects, pill burden and barrier to resistance. As an example, at baseline, we prioritized newer protease inhibitors (PIs) such as DRV over older PIs such as IDV. Given that lower 'weighted scores' represent more preferred regimens, this type of preference was implemented through numerical 'penalties' or 'prioritizations' that were added or subtracted to an individual ARV's net utility. Drug interactions were assessed as numeric penalties based on the degree of interaction with each ARV. For example, an interaction between rifampin and a PI was assessed a severe penalty, in essence conferring a 'contraindication.' Similarly, comorbidities resulted in additional utility weights (e.g., ABC is assessed a numeric penalty in the presence of known cardiovascular disease). Utility weights for comorbidities and co-medications were developed by our team with consultation from HIV clinicians and pharmacists. The site currently includes 30 comorbidities and 210 co-medications, with the complete list available on the website. We note that HIV-ASSIST was not designed to be a comprehensive drug-interaction checker and is based primarily on drug-interaction information in the DHHS guidelines. These individual ARV utilities were then numerically summed to generate an aggregate utility weight for an ARV regimen, calibrated to create a 'base-score' that largely reflects current guidelines for ARV-naive patients (e.g., BIC/TAF/FTC has a weighted score of 1.0 in the absence of any other modifying factors).

The ARV regimen 'Weighted Score' was then further modulated using a multi-attribute utility function that incorporated consideration of viral load, CD4 cell count, pill burden, ARV treatment history and current viral suppression or viremia. In the 'base-case' without modifying factors, a score of 1.0 reflects preferred regimens for ARV-naive patients as it relates to the composite outcome of interest (i.e., viral suppression and tolerability) with higher weighted scores (e.g., > 2.0) reflecting reduced preference. For example, while EFV/TDF/FTC is a regimen with strong evidence for achieving viral suppression, its net 'base-score' is higher (i.e., less preferred) than that of DTG+TAF/FTC on the basis of greater tolerability (e.g., greater discontinuations compared to INSTIs) and lower barrier to resistance.[2,3] Pill burden and dosing frequency were factored into the utility function using a mathematical formula that prioritizes single pill once/daily regimens. Regimen 'activity' incorporated the mutation penalties in the Stanford

HIV Database; we developed a mathematical formula (available online at https://www.hivassist.com) to numerically penalize regimens on the basis of their aggregate mutation scores. The formula was refined over the development process to reflect relative prioritization of regimens under varying case scenarios.

For ARV-experienced patients (suppressed or viremic), we developed decision rules to reflect current guidance based on DHHS and IAS recommendations, as well as through key informant discussions at Johns Hopkins University and Brigham and Women's Hospital. Overall, the utility function sought to mathematically quantify treatment principles identified in the ARV regimen selection process. Utility functions were developed to reflect treatment principles within the DHHS guidelines for consideration of regimens after treatment failure, by class. For example, the function numerically prioritizes PI or INSTI-based regimens given a history of treatment failure to NNRTI-based regimens.[2,4,5] Similar functions were developed for consideration of treatment simplification in ARV-experienced patients with a suppressed viral load, reflecting current DHHS guidance. For example, the algorithm suggests DTG/RPV as a simplification strategy for patients suppressed on stable ARV regimens. Additional HIV-ASSIST utility functions were developed to describe switch strategies prioritizing regimens with decreased pill burden or dosing frequency (while preserving overall regimen efficacy).

The HIV-ASSIST algorithm also heavily weighed the number of active drugs in each regimen as calculated by the individual ARV 'activity score' utility weight, in order to emphasize the ARV objective of achieving virologic suppression. Regimens with decreasing number of active drugs are exponentially penalized, especially if the patient is experiencing ongoing viremia. The algorithm consequently eliminated regimens containing ARVs with high-level known genotypic or assumed mutations (e.g., if history of treatment failure to a particular regimen). We created specific decision rules to allow for consideration of mutations that resulted in hypersensitization of other ARVs within the regimen. For example, a regimen consisting of DTG+TAF/FTC is considered in spite of an M184V mutation (conferring high-level emtricitabine resistance) if the TAF and DTG are fully-active. We developed a user-defined input function to further scale that preference, reflecting differences in provider practice (e.g., comfort with regimens with two active drugs versus requirement for three active drugs).

A comprehensive listing of the major decision rules incorporated into the HIV-ASSIST algorithm are available on the HIV-ASSIST website under the Methodology subheading. Additionally, a listing of all available comorbidities and comedications are available on the main HIV-ASSIST tool page.

Educational content

Relying on DHHS guidelines, package inserts, and available literature, we sought to summarize relevant guidelines on usage of each regimen for both ARV-naïve and experienced patients, as well as to compile available clinical trial data (example in Supplementary Figure 1). We additionally included information on dosing and administration, including adjustments for renal or hepatic insufficiency (example in Supplementary Figure 2). Specific algorithm details are also available for each ARV regimen in an effort to promote transparency of the HIV-ASSIST decision making process. Finally, we created a printable 'narrative report' whereby the clinician-user can compare, in prose form, the top-ranked HIV-ASSIST and the regimen selected by the user (Supplementary Figure 3).

Results

Primary Outcome: Concordance with expert ARV prescribing preferences

Supplementary Table 1 shows results of a validation study to assess concordance between HIV-ASSIST algorithm-generated ranked outputs and ARV prescribing preferences for a cohort of 17 experienced HIV providers (8 from JHH, 3 from BWH/MGH, and 6 from UCSF; the majority of whom had 10+ years of experience managing HIV). Additional results are described in the manuscript text.

Secondary Outcome: Analysis of contraindicated regimens

When presented with the top five HIV-ASSIST ranked outputs for each case, zero respondents considered the first ranked HIV-ASSIST output to be contraindicated/unacceptable in five out of the ten (50%) of case scenarios (including three of the four ARV-naïve scenarios [Scenarios #1–3] and two out of the three virally-suppressed scenarios [Scenarios #9–10]). Among the remaining five cases (Scenarios #4–8), between one to three of the 17 respondents (6–18%) considered the HIV-ASSIST top-ranked output to be contraindicated. However, among those same cases, between two to eleven of the 17 participants (12–65%) had reported their free-response ARV preference to be the same as the HIV-ASSIST top-ranked output, demonstrating provider heterogeneity in ARV selection. There was also heterogeneity amongst provider rationale in determining which regimens were 'medically contraindicated' (see Supplementary Table 2). The most commonly cited reasons for considering an ARV regimen to be contraindicated were having fewer than three active drugs, or regimens containing large pill sizes in situations where patients had demonstrated difficulty with compliance. In some instances, providers deemed regimens contraindicated due to potential dosing and drug interactions (e.g., rifampin with use of raltegravir; usage of EFV/TDF/FTC with rifampin) that were inconsistent with current guidelines (e.g., DHHS guidelines define acceptable use of rifampin with raltegravir if the latter is used at twice-a-day dosing; in contrast to package insert, DHHS and other guidelines suggest no dosing changes to fixed dosed combination of EFV/TDF/FTC with rifampin).

Supplementary References

1. Appendix A: Key to Acronyms. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.* US Department of Health and Homeland Services (DHHS). https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/292/drug-name-abbreviations.
2. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. US Department of Health and Human Services (DHHS). https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
3. Walmsley S, Baumgarten A, Berenguer J, et al. Brief Report: Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial. *J Acquir Immune Defic Syndr.* 2015;70(5):515-519.
4. Boyd MA, Amin J, Mallon PW, et al. Body composition and metabolic outcomes after 96 weeks of treatment with ritonavir-boosted lopinavir plus either nucleoside or nucleotide reverse transcriptase inhibitors or raltegravir in patients with HIV with virological failure of a standard first-line antiretroviral therapy regimen: a substudy of the randomised, open-label, non-inferiority SECOND-LINE study. *Lancet HIV.* 2017;4(1):e13-e20.
5. Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med.* 2014;371(3):234-247.

Supplementary Figure 1

Sample of clinical evidence summary and educational sheet

Other Considerations

ABC

- May see hypersensitivity reaction in patients who are not HLA-B*5701 negative
- Dosing does not need to be adjusted for patients with renal insufficiency

DTG

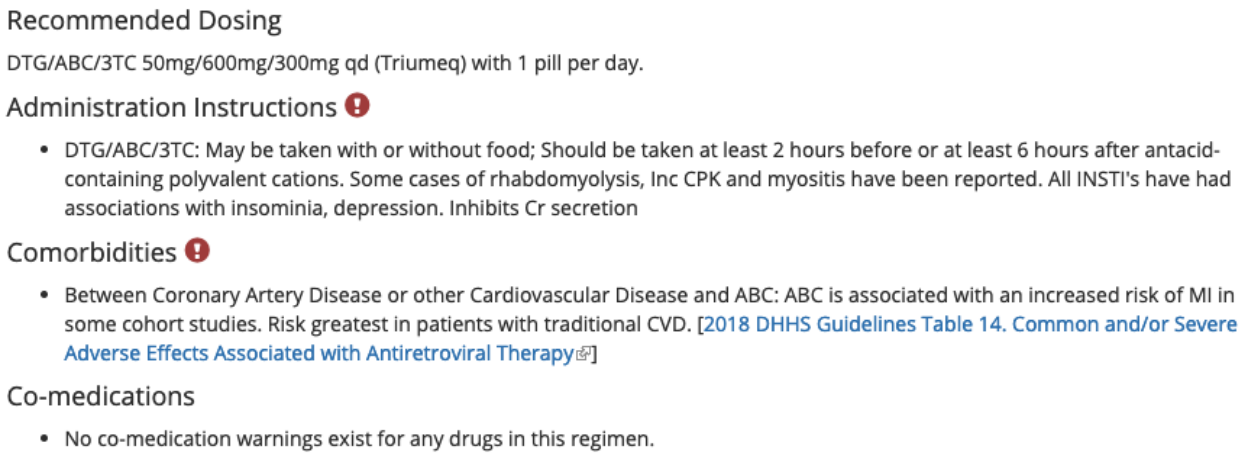
- Lowest risk of resistance with virological failure among INSTIs
- Relatively few drug interactions
- Can be taken with or without food (but not with polyvalent ions, which may be found in antacids, laxatives, and mineral supplements)
- May raise serum creatinine
- Largest tablet among co-formulated single-pill regimens
- Possible side effects include insomnia, headache, and (rarely) hypersensitivity reaction
- Use caution in women of child bearing age, based on limited reports of neural tube defects. DHHS recommends documenting negative pregnancy test prior to initiation. Women should be counseled about switching to alternatives if pregnant and within 8 weeks since LMP. [1]

Efficacy in Clinical Trials

Trial Name	Drugs Compared	Participants	Results
SINGLE	ABC/3TC/DTG vs. TDF/FTC/EFV	833 tx-naive	At week 48, the proportion of participants with an HIV-1 RNA level of less than 50 copies per milliliter was significantly higher in the ABC/3TC/DTG group than in the TDF/FTC/EVF group (88% vs. 81%). Was due primarily to discontinuations because of adverse events (2% in the ABC/3TC/DTG group and 10% in the TDF/FTC/EVF group). At week 144, ABC/3TC/DTG remained superior (71% vs 63% viral suppression) [2] [3] [4]
ARIA	ABC/3TC/DTG vs. TDF/FTC+/ATV/r	495 tx-naive women	At 48 weeks, ABC/3TC/DTG was superior in terms of virologic suppression (82% vs 71%). There were fewer virological nonresponses and fewer discontinuations due to adverse events in the ABC/3TC/DTG arm [5].
FLAMINGO	2 NRTIs plus DTG or DRV/r	484 tx-naive	At 48 weeks, DTG outperformed DRV/r (viral suppression 90% vs 83%). Discontinuation due to adverse effects was higher in the DRV/r group than the DTG group (2% vs 4%, respectively), which contributed to the difference in the response rate. DTG continued to outperform DRV/r at 96 weeks (viral suppression 80% vs 66%) [6] [7].
SPRING-2	2 NRTIs plus DTG or RAL	822 tx-naive	At 48 and 96 weeks, DTG was non-inferior to RAL (88% vs 85% viral suppression at 48 weeks, and 81% vs 76% at 96 weeks), with a similar safety profile [8] [9].
STRIIVING	ABC/DTG/3TC vs current ART	553 tx-experienced	At week 24, switching to ABC/DTG/3TC from current ART regimen was found to be noninferior to remaining on current ART (85% switched vs 88% remained virally suppressed). At week 48, 83% of the early-switch group remained virologically suppressed, while 92% of the late-switch group were virally suppressed. ABC/DTG/3TC found to be noninferior to continuing current ART and should be considered as an option when switching virally suppressed patients[10]

Supplementary Figure 2

Sample of dosing and administration guidance of DTG/ABC/3TC for a patient with coronary artery disease (CAD) taking aspirin and metoprolol



Supplementary Figure 3

Sample of narrative report and algorithm transparency for a patient with ongoing viremia on EFV/TDF/FTC, without any documented mutations

Preferred regimen based on the HIV-ASSIST algorithm: BIC/TAF/FTC

BIC/TAF/FTC had the lowest weighted score (1) among all regimens we evaluated. In general, lower HIV-ASSIST weighted scores are considered preferable. Your patient may have other considerations we did not factor in and this report should not be considered a statement of likely success with this patient; please use clinical judgement in making final ART selections. Other regimens you may wish to consider are listed below. A full list of ART regimen scores can be found by clicking the Expert tab above.

Among treatment naive patients, this regimen had a 'base-score' of 1, and is considered 'Recommended' in the IAS guidelines and 'Recommended--Most*' in the DHHS guidelines.

Regimen	Weighted Score	Active Drugs	Total Pills	Max Freq
BIC/TAF/FTC	1	2	1	qd

The rationale behind why this regimen was chosen by our algorithm as the most appropriate is shown below:

Score (Change)	Explanation
1 (Base Score)	Base Score for BIC/TAF/FTC
1 (+0)	Pill burden: All regimens with more than one pill once per day incur a pill burden penalty. This regimen received a penalty of +0 using the formula 0.5 * (1 time(s) daily - 1) + 0.2 * (1 total pill(s) - 2)
1 (+0)	Mutations: This regimen was penalized +0 for drug mutations using the formula 2^1 * 0.02 * 0. According to the Stanford Database, individual drug mutation scores were : FTC: 60, TAF: -10, BIC: 0
0.5 (-0.5)	Non-suppressed viral load: We prioritized switching to 2 NRTI + (DTG or BIC) +/- another ARV after treatment failure on an NNRTI regimen
1 (+0.5)	Non-suppressed viral load: In general, we prioritized regimens with at least 3 active drugs. However, we also gave some preference to two-drug regimens containing fully-active DRV, DTG, or BIC. (Active drugs in this regimen: 2).
1 (Final)	**Final weighted score**

#	Case Characteristics	Top 5 HIV-ASSIST Ranked Outputs	HIV-ASSIST Weighted Score	Participant Free Response (n/N)	% Concordance, Rank 1 (*)	% Concordance, Ranks 1-5 (*)	Median Diff. from HIV-ASSIST Score (IQR)
1	**CD4** <100, **HIV VL** >100k **Tropism:** R5 **Co-morbidities:** none **Co-medications:** none **Genotype:** no mutations **Treatment Failure Hx:** naïve	BIC/TAF/FTC DTG/ABC/3TC DTG + TAF/FTC EVG/c/TAF/FTC DRV/c/TAF/FTC	1 1 1 1.3 1.5	BIC/TAF/FTC (15/17) DTG + TAF/FTC (2/17)	88%	100%	0 (0)
2	**CD4** >200, **HIV VL** 50-100k **Tropism:** R5 **Co-morbidities:** hypertension, hyperlipidemia **Co-medications:** aspirin, atorvastatin, metoprolol, lisinopril **Genotype:** no mutations **Treatment Failure Hx:** naïve	DTG + TAF/FTC BIC/TAF/FTC RPV/TAF/FTC RAL (HD) + TAF/FTC DTG/ABC/3TC	0.75 1 1.9 2 2.25	DTG + TAF/FTC (2/17) BIC/TAF/FTC (15/17)	12%	100%	0.25 (0.25)
3	**CD4** >200, **HIV VL** >100k **Tropism:** R5 **Co-morbidities:** diabetes, depression **Co-medications:** sertraline, metformin **Genotype:** no mutations **Treatment Failure Hx:** naïve	BIC/TAF/FTC EVG/c/TAF/FTC DTG/ABC/3TC DTG + TAF/FTC DRV/c/TAF/FTC	1.35 1.4 1.6 1.6 1.75	BIC/TAF/FTC (16/17) DTG + TAF/FTC (1/17)	94%	100%	0 (0)
4	**CD4** <50, **HIV VL** 50-100k **Tropism:** R5 **Co-morbidities:** pulmonary tuberculosis **Co-medications:** rifampin, isoniazid, pyrazinamide, ethambutol **Genotype:** no mutations **Treatment Failure Hx:** naïve	EFV/TDF/FTC DTG/ABC/3TC (+DTG qhs) DTG (bid) + TDF/FTC RAL (bid) + TDF/FTC EFV + ABC/3TC	1.9 2 2.4 3 3.35 -	EFV/TDF/FTC (4/17) DTG/ABC/3TC (+ DTG qhs) (1/17) DTG (bid) + TDF/FTC (11/17) *DTG (bid) + TAF/FTC (1/17)* [a]	24% (25%)	94% (100%)	0.5 (0.3–0.5)
5	**CD4** <200, **HIV VL** >100k **Tropism:** dual/mixed **Co-morbidities:** none **Co-medications:** none **Genotype:** M184V **Treatment Failure Hx:** EFV/TDF/FTC, DTG/ABC/3TC	DTG + DRV/c/TAF/FTC DRV/c/TAF/FTC DTG + TAF/FTC DRV/c + BIC/TAF/FTC DRV/c + DTG/ABC/3TC	0.5 1 1 1.5 1.95 *2* *2* *3.2* -	DTG + DRV/c/TAF/FTC (2/16) DRV/c/TAF/FTC (6/16) DTG + TAF/FTC (1/16) DRV/c + BIC/TAF/FTC (2/16) [b] *BIC/TAF/FTC (3/16)* *DRV/c + DTG (1/16)* *ETR + DRV/r + DTG (1/16)* *DRV/c + DOR + DTG (excluded)* [c]	13%	69%	0.5 (0.5–1.5)
6	**CD4** <50, **HIV VL** >100k **Tropism:** dual/mixed **Co-morbidities:** none **Co-medications:** none **Genotype:** M184V, M41L, T215Y **Treatment Failure Hx:** EFV/TDF/FTC, AZT/3TC + LPV/r	DRV/c + BIC/TAF/FTC DTG + DRV/c/TAF/FTC DRV + EVG/c/TAF/FTC DTG + DRV/c DTG/RPV + DRV/c	2.4 2.4 2.75 2.75 3 *3.65*	DRV/c + BIC/TAF/FTC (4/17) DTG + DRV/c/TAF/FTC (6/17) DTG + DRV/c (2/17) DTG/RPV + DRV/c (4/17) *DTG + TAF/FTC (1/17)*	24%	94%	0 (0–0.6)

7	**CD4** >200, **HIV VL** 1000-5000 **Tropism:** R5 **Co-morbidities:** severe gastritis **Co-medications:** pantoprazole, Tums **Genotype:** M184V, Y143H **Treatment Failure Hx:** TDF/FTC + RAL, currently on DTG/ABC/3TC *Reports difficulty with pill size	DRV/c/TAF/FTC DTG (bid) + DRV/c/TAF/FTC DTG (bid) + DRV/c DRV/c + BIC/TAF/FTC DTG (bid) + TAF/FTC	1.3 1.95 2.8 3.25 3.4 *3.8* -	DRV/c/TAF/FTC (6/16) DTG (bid) + DRV/c/TAF/FTC (4/16) DTG (bid) + DRV/c (1/16) DRV/c + BIC/TAF/FTC (2/16) DTG (bid) + TAF/FTC (1/16) *BIC/TAF/FTC (2/16)* *DOR + DTG + TAF/FTC (excluded)* [c]	38%	88%	0.65 (0–1.95)
8	**CD4** >200, **HIV VL** undetected **Tropism:** R5 **Co-morbidities:** none **Co-medications:** temazepam **Genotype:** K65R, T215Y, K103N, V32I, I47A **Treatment Failure Hx:** AZT/3TC + LPV/r; currently on TAF/FTC + DTG + DRV/r *Reports difficulty with pill burden	DTG/RPV DTG + MVC (bid) MCV (bid) + DTG/RPV RAL (HD) + RPV RAL (bid) + MVC (bid)	1 1.7 1.8 3 3.45 - - - -	DTG/RPV (11/16) [d] MCV (bid) + DTG/RPV (2/16) *DTG/RPV + DRV/c (1/16)* [e] *DTG + DRV/c (1/16)* [e] *DTG/ABC/3TC + DRV/c (1/16)* [e] *DOR + BIC/TAF/FTC (excluded)* [c]	69% (85%)	81% (100%)	0 (0)
9	**CD4** >200, **HIV VL** undetected **Tropism:** R5 **Co-morbidities:** hypertension, osteoporosis **Co-medications:** lisinopril **Genotype:** M184V **Treatment Failure Hx:** currently on EVG/c/TDF/FTC	DTG/RPV DRV/c + DTG/RPV BIC/TAF/FTC DTG + TAF/FTC DTG + DRV/c	1 1.1 1.5 1.75 1.75	DTG/RPV (7/17) BIC/TAF/FTC (9/17) [f] DTG + DRV/c (1/17)	41%	100%	0 (0–0.5)
10	**CD4** >200, **HIV VL** undetected **Tropism:** dual/mixed **Co-morbidities:** none **Co-medications:** none **Genotype:** K103N, M184V, F121Y **Treatment Failure Hx:** EFV/TDF/FTC; TDF/FTC + RAL; currently on DTG/ABC/3TC + DRV/c *Reports difficulty with pill size	DRV/c + RPV/TAF/FTC DRV/c/TAF/FTC DRV/c + BIC/TAF/FTC RPV + BIC/TAF/FTC DTG + DRV/c/TAF/FTC	1.8 1.8 1.9 1.95 2.6 *2.8* *5.45* *7.3*	DRV/c + RPV/TAF/FTC (1/17) DRV/c/TAF/FTC (3/17) DRV/c + BIC/TAF/FTC (4/17) RPV + BIC/TAF/FTC (2/17) DTG + DRV/c/TAF/FTC (4/17) *DRV/c + DTG/RPV + DTG (qhs) (1/17)* *DTG (bid) + DRV/c (1/17)* *DTG/RPV + DTG (qhs) (1/17)*	6%	82%	0.15 (0.1–0.8)

Supplementary Table 1. Assessment of HIV-ASSIST Recommendation Concordance with Free Responses from Experienced HIV Clinicians

All drugs are dosed once daily unless otherwise noted. Italicized regimens are free responses not ranked within the top five by HIV-ASSIST. Abbreviations: VL – viral load; Hx - history; bid - twice daily; qhs - additional nightly dose; HD - once-daily high-dose formulation (of raltegravir).

[a] While some data exists on using TAF with rifampin, HIV-ASSIST algorithms drew upon current guidelines recommending against usage at the time of the study.

[b] If both cobicistat- and ritonavir-containing regimens (with otherwise identical ARVs) are ranked by HIV-ASSIST, only cobicistat-containing regimens are listed for simplicity.

[c] Doravirine (DOR)-containing free responses are listed but not included in quantitative analyses, as DOR was not yet included in HIV-ASSIST at the time of the study.

[d] One respondent provided two responses: DTG/RPV as well as DTG/RPV + boosted DRV, which is ranked 6th by HIVASSIST; only DTG/RPV is shown in the table.

[e] HIV-ASSIST algorithms required bid boosted-Darunavir (DRV) in the presence of protease inhibitor resistance mutations. Once daily DRV/c containing regimens were excluded by current HIV-ASSIST algorithms.

[f] One respondent provided two responses: BIC/TAF/FTC as well as EVG/c/TAF/FTC, which is ranked 27th by HIVASSIST; only BIC/TAF/FTC is shown in the table.

* Parenthetical analyses exclude free responses inconsistent with current DHHS guidelines (for specific reasons categorized as a or e above)

#	Case Characteristics	Top 5 HIV-ASSIST Ranked Outputs	HIV-ASSIST Weighted Score	% Considered Contraindicated (N = 17)	Reasons for Contraindication
1	**CD4** <100, **HIV VL** >100k **Tropism:** R5 **Co-morbidities:** none **Co-medications:** none **Genotype:** no mutations **Treatment Failure Hx:** naïve	BIC/TAF/FTC DTG/ABC/3TC DTG + TAF/FTC EVG/c/TAF/FTC DRV/c/TAF/FTC	1 1 1 1.3 1.5	0% 0% 0% 0% 6% (1/17)	"increased toxicities associated with PIs"
2	**CD4** >200, **HIV VL** 50-100k **Tropism:** R5 **Co-morbidities:** hypertension, hyperlipidemia **Co-medications:** aspirin, atorvastatin, metoprolol, lisinopril **Genotype:** no mutations **Treatment Failure Hx:** naïve	DTG + TAF/FTC BIC/TAF/FTC RPV/TAF/FTC RAL (HD) + TAF/FTC DTG/ABC/3TC [a]	0.75 1 1.9 2 2.25	0% 0% 0% 0% -	-
3	**CD4** >200, **HIV VL** >100k **Tropism:** R5 **Co-morbidities:** diabetes, depression **Co-medications:** sertraline, metformin **Genotype:** no mutations **Treatment Failure Hx:** naïve	BIC/TAF/FTC EVG/c/TAF/FTC DTG/ABC/3TC DTG + TAF/FTC DRV/c/TAF/FTC	1.35 1.4 1.6 1.6 1.75	0% 6% (1/17) 6% (1/17) 6% (1/17) 0%	"Genvoya less forgiving… builds mutations, many drug interactions" [no reason given] [no reason given]
4	**CD4** <50, **HIV VL** 50-100k **Tropism:** R5 **Co-morbidities:** pulmonary tuberculosis **Co-medications:** rifampin, isoniazid, pyrazinamide, ethambutol **Genotype:** no mutations **Treatment Failure Hx:** naïve	EFV/TDF/FTC DTG/ABC/3TC (+ DTG qhs) DTG (bid) + TDF/FTC RAL (bid) + TDF/FTC EFV + ABC/3TC [a]	1.9 2 2.4 3 3.35	6% (1/17) 6% (1/17) 6% (1/17) 6% (1/17) -	"In patients >50kg, a dose of [EFV] 800mg/day may be considered" [b] [no reason given] [no reason given] "can't use RAL with Rifampin" [c] -
5	**CD4** <200, **HIV VL** >100k **Tropism:** dual/mixed **Co-morbidities:** none **Co-medications:** none **Genotype:** M184V **Treatment Failure Hx:** EFV/TDF/FTC, DTG/ABC/3TC	DTG + DRV/c/TAF/FTC DRV/c/TAF/FTC DTG + TAF/FTC DRV/c + BIC/TAF/FTC DRV/c + DTG/ABC/3TC [a]	0.5 1 1 1.5 1.95	6% (1/17) 12% (2/17) 29% (5/17) 6% (1/17) -	"using all 3 classes of drugs is unnecessary/excessive" "2 active agents" "2 active agents" "worry about failure" "currently failing DTG regimen" "using all 3 classes of drugs is unnecessary/excessive" -
6	**CD4** <50, **HIV VL** >100k **Tropism:** dual/mixed **Co-morbidities:** none **Co-medications:** none **Genotype:** M184V, M41L, T215Y **Treatment Failure Hx:** EFV/TDF/FTC, AZT/3TC + LPV/r	DRV/c + BIC/TAF/FTC DTG + DRV/c/TAF/FTC DRV + EVG/c/TAF/FTC DTG + DRV/c DRV/c + DTG/RPV	2.4 2.4 2.75 2.75 3	12% (2/17) 0% 6% (1/17) 12% (2/17) 12% (2/17)	"Biktarvy in combo with other meds is not recommended in DHHS" [no reason given] "only 2 active drugs" "no data on DRV/c in this setting" "RPV not rec'd if baseline VL > 100k" "viremic on EFV"

	CD4 >200, **HIV VL** 1000-5000 **Tropism:** R5 **Co-morbidities:** severe gastritis **Co-medications:** pantoprazole, Tums **Genotype:** M184V, Y143H **Treatment Failure Hx:** TDF/FTC + RAL, currently on DTG/ABC/3TC *Reports difficulty with pill size	DRV/c/TAF/FTC DTG (bid) + DRV/c/TAF/FTC DTG (bid) + DRV/c [a] DRV/c + BIC/TAF/FTC DTG (bid) + TAF/FTC	1.3 1.95 2.8 3.25 3.4	18% (3/17) 6% (1/17) - 18% (3/17) 18% (3/17)	"2 active agents" "only 1.5 drugs" "large pill size" "large pill size" - "would not use Biktarvy in combo with other agents" "large pill size" "INSTI + NRTI only partially active" "2 active agents" "only 1.5 drugs"
7					
	CD4 >200, **HIV VL** undetected **Tropism:** R5 **Co-morbidities:** none **Co-medications:** temazepam **Genotype:** K65R, T215Y, K103N, V32I, I47A **Treatment Failure Hx:** AZT/3TC + LPV/r; currently on TAF/FTC + DTG + DRV/r *Reports difficulty with pill burden	DTG/RPV DTG + MVC (bid) MCV (bid) + DTG/RPV RAL (HD) + RPV RAL (bid) + MVC (bid)	1 1.7 1.8 3 3.45	12% (2/17) 24% (4/17) 12% (2/17) 24% (4/17) 41% (7/17)	"only 2 active drugs" "only 2 active drugs" "no data, BID drug" "no data, 2 weak drugs" "lower barrier to resistance with RAL" "only 2 active drugs" "no data" "drug interactions" 'high rates of failure in ROCnRAL" "only 2 active drugs"
8					
	CD4 >200, **HIV VL** undetected **Tropism:** R5 **Co-morbidities:** hypertension, osteoporosis **Co-medications:** lisinopril **Genotype:** M184V **Treatment Failure Hx:** currently on EVG/c/TDF/FTC	DTG/RPV DRV/c + DTG/RPV BIC/TAF/FTC DTG + TAF/FTC DTG + DRV/c	1 1.1 1.5 1.75 1.75	0% 18% (3/17) 12% (2/17) 6% (1/17) 12% (2/17)	 "3 classes of drugs unnecessary" "2 active agents" "no data supporting use of BIC salvage with resistance" "2 active agents" "NRTI-sparing regimen unnecessary" "not necessary"
9					
	CD4 >200, **HIV VL** undetected **Tropism:** dual-mixed **Co-morbidities:** none **Co-medications:** none **Genotype: K103N,** M184V, F121Y **Treatment Failure Hx:** EFV/TDF/FTC; TDF/FTC + RAL; currently on DTG/ABC/3TC + DRV/c *Reports difficulty with pill size	DRV/c + RPV/TAF/FTC DRV/c/TAF/FTC DRV/c + BIC/TAF/FTC RPV + BIC/TAF/FTC DTG + DRV/c/TAF/FTC	1.8 1.8 1.9 1.95 2.6	0% 18% (3/17) 18% (3/17) 18% (3/17) 6% (1/17)	 "inappropriate when requested small pills" "2 active agents" "use of Biktarvy in combo with other ARVs in salvage not studied" "use of Biktarvy in combo with other ARVs in salvage not studied" "inappropriate when requested small pills"
10					

Supplementary Table 2. Evaluation of HIVASSIST Recommendations Considered Contraindicated by Experienced HIV Clinicians

[a] Due to iterative changes made to the HIVASSIST algorithms at the time of this study, for some case scenarios (#2, 4, 5, and 7) not all of the currently top-ranked HIVASSIST outputs were included as answer choices in the validation survey. Un-included regimens (four in total) are indicated above.

[b] While the package insert has suggested a dose adjustment when combined with rifampin based on PK considerations, current DHHS guidelines suggest no dosing adjustments (EFV 600mg daily) in combination with rifampin, based on data that suggests continued efficacy without increased rates of treatment failure with standard fixed dosed combination EFV/TDF/FTC[2]

[c] Dosing guidelines are available for rifampin in combination with raltegravir (800mg bid) within DHHS guidelines[2]