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Changes in drug interaction profiles for first-line HIV therapy over the 20 years of the Liverpool Drug Interaction website

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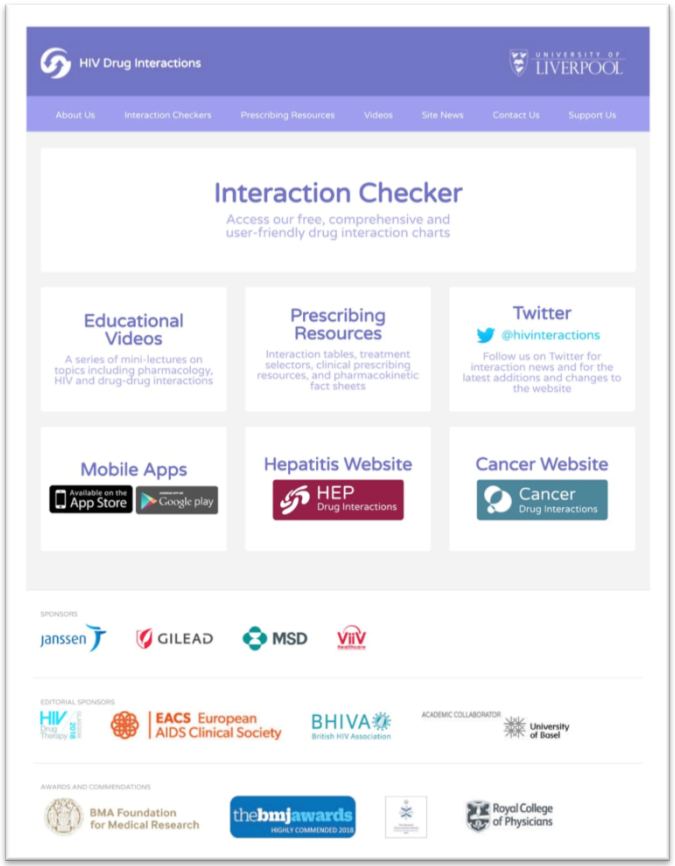
20 Years Ago …



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Drug Interactions with Protease Inhibitors

Drugs are arranged alphabetically within the following classes:

Analgesics | Antihistamines | Anxiolytics/Hypnotic/Sedative | Immunosuppressants
Antiarrhythmics | Antimigraine | Beta Blockers | Lipid Lowering
Antibacterials | Antineoplastics | Bronchodilators | Neuroleptics
Anticoagulant | Antiprotozoals | Calcium Channel Antagonists | Oral Hypoglycaemics
Anticonvulsants | Antipsychotics | Erectile Dysfunction Agents | Steroids
Antidepressants | Antivirals | Gastrointestinal Agents (including anti-emetics) | Stimulants
Antifungals

Hint: Use your browser's "find in page" feature to locate a particular drug.

Key to symbols:

- These drugs should not be coadministered
- Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.
- No clinically significant interaction.
- There are no clear data, actual of theoretical, to indicate whether an interaction will occur.

Clicking on the symbol within a table will give further information on the interaction where available

Analgesics		Indinavir	Ritonavir	Saquinavir	Nelfinavir
	aspirin	▲	▲	▲	▲
	paracetamol	▲	▲	▲	▲
NSAIDs	ibuprofen	▲	■	▲	▲
	piroxicam	▲	●	▲	▲
narcotic / morphinomimetic	dextropropoxyphene	■	●	■	■
	diamorphine	▲	■	▲	▲
	fentanyl	■	■	■	■
	meperidine (pethidine)	■	●	■	■
	methadone	■	■	■	■
	morphine	▲	■	▲	▲

Drug Interactions with NNRTIs

Drugs are arranged alphabetically within the following classes:

Analgesics | Antihistamines | Anxiolytics/Hypnotic/Sedative | Immunosuppressants
Antiarrhythmics | Antimigraine | Beta Blockers | Lipid Lowering
Antibacterials | Antineoplastics | Bronchodilators | Neuroleptics
Anticoagulant | Antiprotozoals | Calcium Channel Antagonists | Oral Hypoglycaemics
Anticonvulsants | Antipsychotics | Erectile Dysfunction Agents | Steroids
Antidepressants | Antivirals | Gastrointestinal Agents (including anti-emetics) | Stimulants
Antifungals

Hint: Use your browser's "find in page" feature to locate a particular drug.

Key to symbols:

- These drugs should not be coadministered
- Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.
- No clinically significant interaction.

Analgesics		Delavirdine	Efavirenz	Nevirapine
	aspirin	▲	▲	▲
	paracetamol	▲	▲	▲
NSAIDs	ibuprofen	▲	▲	▲
	piroxicam	■	▲	▲
narcotic / morphinomimetic	dextropropoxyphene	■	▲	▲
	diamorphine	▲	▲	▲
	fentanyl	■	▲	▲
	meperidine (pethidine)	■	▲	▲
	methadone	■	■	■
	morphine	▲	▲	▲

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Drug Interactions Website - Then and Now

1999

- 7 ARV drugs
- 142 comedications
- 994 interactions
- ~30% interactions clickable for further information
  (data available for PIs only)

2019

- 36 ARV drugs and/or combinations
- 729 comedications
- 26244 interactions
- 100% interactions clickable for further information

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UK Treatment Guidelines, 2000 (BHIVA)

Regimen	Recommendation	Advantages	Disadvantages
Primary HIV infection			
Clinical trial	Recommended		
HAART	Consider		
No therapy	Consider		
Chronic HIV infection			
2NAs + PI[1]	Recommended	(1) RCT evidence with clinical endpoints (2) Evidence of efficacy in late disease (3) Long-term follow-up	(1) Toxicity common (2) High pill burden (3) Drug interactions
2NAs + 2PIs[2]	Recommended	(1) Easier adherence (2) Better pharmacokinetics	(1) No clinical endpoint data (2) Less comparative surrogate marker data (3) Possible increased toxicity and drug interactions
2NAs + NNRTI[3]	Recommended	(1) Equivalent or superior efficacy in surrogate marker trials at 72 weeks (2) Easier adherence (3) Less known toxicity than PI-containing regimen	(1) No clinical endpoint data (2) Lack of surrogate marker data in late disease (3) Shorter follow-up (4) Little evidence of immune reconstitution (5) Single mutations may lead to cross-class resistance
3NAs[4]	Under evaluation	(1) Spares PIs and NNRTIs (2) Fewer drug interactions	(1) No clinical endpoint data (2) Short-term surrogate marker data only (3) Less effective at high viral load

[1]Hard-gel saquinavir should not be used as the sole PI. There are fewer data concerning use of saquinavir soft-gel in this context than for other PIs. [2]Primary reason for combining PIs is to improve pharmacokinetics. Suggested regimens: low-dose ritonavir (i.e. 100–400 mg) with saquinavir, indinavir or amprenavir. [3]Recommended NNRTIs are efavirenz or nevirapine. In one controlled trial, efavirenz was as effective in patients with viral loads > 100 000 copies/mL as in those with < 100 000 copies/mL. There are fewer data from controlled trials to address this issue for nevirapine. [4]May be suitable for patients with viral load ⩽100 000 copies/mL. Two regimens have been studied: abacavir + lamivudine + zidovudine and stavudine + didanosine + lamivudine.

Table 5 Currently available protease inhibitors

Protease inhibitor	Dose	Frequency	Daily pill burden	Dietary restrictions	Major side-effects
Nelfinavir	750 mg or 1250 mg	tds bd[1]	9 tablets 10 tablets	with food with food	Mild to moderate diarrhoea
Indinavir	800 mg	tds[2]	6 capsules	empty stomach	Renal stones, crystalluria & sludge, hyperbilirubinaemia[3]
Ritonavir	600 mg[4]	bd	12 capsules	none*	Taste perversion, nausea, diarrhoea, perioral tingling
Saquinavir (soft-gel)[5]	1200 mg[1] or 1800 mg1	tds bd	18 capsules 18 capsules	with food with food	Nausea, diarrhoea, abdominal pain, headache
Amprenavir[6]	1200 mg	bd	16 capsules	none*	Nausea, diarrhoea, rash, headache, perioral tingling

[1]Dose currently unlicensed. [2]Recent data suggest that the bd regimen is less effective in suppressing viral load. [3]Progressive deterioration of renal function may be associated with long-term use. [4]Often used at lower doses (e.g. 100–400 mg bd) as part of a dual PI-containing HAART regimen. [5]The hard-gel formulation is still available for use in combination with ritonavir. [6]Not yet licensed in Europe. bd, twice a day; tds, three times a day. *Can take after food to prevent nausea.

Table 6 Currently available non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTI	Dose	Frequency/ day	Daily pill burden	Dietary restrictions	Major side-effects
Efavirenz	600 mg	once[1]	3 capsules	none	Dysphoria C/I: pregnancy
Nevirapine[2]	200 mg	twice	2 tablets	none	Rash, hepatitis
Delavirdine[3]	400 mg	three[4]	12 tablets[4]	none[5]	Rash (usually mild), headache

[1]At night. [2]The initial dose is 200 mg/day for 2 weeks, increasing to 400 mg/day. [3]Delavirdine is not yet licensed in Europe. [4]Larger dose tablets and a twice-daily regimen are expected to be introduced shortly. [5]Dose may be dissolved in cola. C/I, contraindicated.

BHIVA Writing Committee; BHIVA Executive Committee. HIV Med. 2000 Mar;1(2):76-101.

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USA Treatment Guidelines, 2000 (DHHS)

Table IX. Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection

This table provides a guide to the use of available treatment regimens for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens in which clinical trials data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load) and sustained increase in CD4+ T cell count (in most cases over 48 weeks), and favorable clinical outcome (i.e. delayed progression to AIDS and death). Particular emphasis is given to regimens that have been compared directly with other regimens that perform sufficiently well with regard to these parameters to be included in the "strongly recommended" category. Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

It is important to note that all antiretroviral agents, including those in the 'Strongly Recommended' category, have potentially serious toxic and adverse events associated with their use. The reader is strongly encouraged to consult tables X-XVI while formulating an antiretroviral regimen.

Antiretroviral drug regimens are comprised of one choice each from columns A and B. Drugs are listed in alphabetical, not priority order.

	Column A	Column B
Strongly Recommended	Efavirenz Indinavir Nelfinavir Ritonavir + Saquinavir (SGC* or HGC*)	Stavudine + Lamivudine Stavudine + Didanosine Zidovudine + Lamivudine Zidovudine + Didanosine
Recommended as an Alternative	Abacavir Amprenavir Delavirdine Nelfinavir + Saquinavir-SGC Nevirapine Ritonavir Saquinavir-SGC	Didanosine + Lamivudine Zidovudine + Zalcitabine
No Recommendation; Insufficient Data*	Hydroxyurea in combination with other antiretroviral drugs Ritonavir + Indinavir Ritonavir + Nelfinavir	
	Column A	**Column B**
Not Recommended; Should Not Be Offered (All monotherapies, whether from column A or B***)	Saquinavir-HGC****	Stavudine + Zidovudine Zalcitabine + Lamivudine Zalcitabine + Stavudine Zalcitabine + Didanosine

* Saquinavir-SGC, soft-gel capsule (Fortovase); Saquinavir-HGC, hard-gel capsule (Invirase).

** This category includes drugs or combinations for which information is too limited to allow a recommendation for or against use.

*** Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high CD4 T cell counts to prevent perinatal transmission, as discussed under "Considerations in the Pregnant Woman".

**** Use of Saquinavir-HGC (Invirase) is not recommended, except in combination with ritonavir.

Available from https://aidsinfo.nih.gov/guidelines/archive/adult-and-adolescent-guidelines

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UK Treatment Guidelines, 2016 (BHIVA)

5.1 Summary recommendations

- We recommend that therapy-naïve PLWH start ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir-boosted protease inhibitor (PI/r), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) (1A).

Table 5.1. Summary recommendations for choice of ART

	Preferred	Alternative
NRTI backbone	Tenofovir-DF and emtricitabine Tenofovir-AF and emtricitabine	Abacavir and lamivudine
Third agent (alphabetical order)	Atazanavir/r Darunavir/r Dolutegravir Elvitegravir/c Raltegravir Rilpivirine	Efavirenz

/r: boosted with ritonavir; /c: boosted with cobicistat

Available from https://www.bhiva.org/HIV-1-treatment-guidelines

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USA Treatment Guidelines, 2018 (DHHS)

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, childbearing potential and use of effective contraception, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, access, and resistance test results. Drug classes and regimens within each class are arranged first by evidence rating, and, when ratings are equal, in alphabetical order.

Recommended Initial Regimens for Most People with HIV
Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.
INSTI plus 2 NRTIs:
Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.
• BIC/TAF/FTC **(AI)**
• DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
• DTG plus tenofovir / FTC (**AI** for both TAF/FTC and TDF/FTC)
• RAL plus tenofovir / FTC (**BI** for TDF/FTC, **BII** for TAF/FTC)

Available from https://aidsinfo.nih.gov/guidelines/archive/adult-and-adolescent-guidelines

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European Treatment Guidelines, 2018 (EACS)

Initial Combination Regimen for ART-naïve Adult HIV-positive Persons

Out of the recommended regimens in persons starting ART, we recommend the use of an INSTI as preferred third agent; tailoring antiretroviral regimens for each individual is essential as other classes of third agents (e.g boosted PI) might be indicated in the presence of resistance or risk of poor adherence.

A) Recommended regimens (one of the following to be selected)[*,**]

* Only drugs currently licensed for initiation of therapy by the EMA are taken into consideration (in alphabetical order).
** Generic HIV drugs are becoming more available and can lead to large cost savings. They can be used as long as they replace the same drug and do not break recommended fixed dose combinations

Regimen	Dosing	Caution	Food requirement
2 NRTIs + INSTI			
ABC/3TC/DTG[a,b,c]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before). DTG 50 mg bid with rifampicin.	None
TAF/FTC[a] or TDF/FTC[a] + DTG[a]	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd		None
TAF/FTC/BIC[a,b]	TAF/FTC/BIC 25/200/50 mg, 1 tablet qd	Al/Ca/Mg-containing antacids should be taken 2h after BIC (fasting conditions) whereas Ca, Mg, Fe or multivitamins supplements can be administered simultaneously with food.	None
TAF/FTC[a] or TDF/FTC[a] + RAL[a,c]	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + RAL 600 mg, 2 tablets qd or + RAL 400 mg, 1 tablet bid	Co-administration of antacids containing Al or Mg not recommended. Co-administration of RAL 1200 mg qd with Ca containing antacids or with Ca, Mg, Fe supplements is not recommended. Use RAL 400 mg bid instead. RAL[c] 400 or 800 mg bid with rifampicin.	None
2 NRTIs + NNRTI			
TAF/FTC/RPV[a,b] or TDF/FTC/RPV[a,b]	TAF/FTC/RPV 25/200/25 mg, 1 tablet qd or TDF/FTC/RPV 300/200/25 mg, 1 tablet qd	Only if CD4 count > 200 cells/µL and HIV-VL < 100,000 copies/mL. PPI contraindicated; H2 antagonists to be taken 12h before or 4h after RPV.	With food
2 NRTIs + PI/r or PI/c			
TAF/FTC[a,b] or TDF/FTC[a,b] + DRV/c[a,c] or + DRV/r[a,c]	TAF/FTC 10/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd or TAF/FTC/DRV/c 10/200/800/150 mg, 1 tablet qd	Monitor in persons with a known sulfonamide allergy.	With food

Available from http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

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First-line Regimens

Historic

- **Recommended combinations**
  - 2 NRTI + PI (boosted or unboosted)
  - 2 NRTI + NNRTI
- **28 regimens**

2 NRTI	PI	NNRTI
ddI + d4T ddI + ZDV 3TC + d4T 3TC + ZDV	IDV NFV RTV IDV/RTV SQV/RTV	EFV NVP

Current

- **Recommended combinations**
  - 2 NRTI + integrase inhibitor
  - 2 NRTI + NNRTI
  - 2 NRTI + boosted PI
- **16 regimens**

2 NRTI	PI	NNRTI	INSTI
FTC/TAF FTC/TDF	ATV/r DRV/r DRV/c	RPV	DTG EVG/c RAL
FTC/TAF			BIC
ABC/3TC			DTG

Available with 2 NRTI as a single tablet once daily

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Assessing the Regimen, Not the Drugs

- Current website lists ARV drugs, ARV combinations and ARV regimens.
- For regimens not listed on the website as a single entity, the components of the regimen were reviewed and the most significant interaction for each of the drugs in the regimen used.
- Complete regimens were assessed against the current panel of comedications.

	EVG/c/FTC/TDF
Amphotericin B	■
Anidulafungin	◆
Caspofungin	◆
Fluconazole	▲
Flucytosine	■
Griseofulvin	■
Itraconazole	■
Ketoconazole	■
Miconazole	◆
Nystatin	◆
Posaconazole	■
Terbinafine	▲
Voriconazole	■

	DRV/c	FTC/TDF	DRV/c/FTC/TDF
Amphotericin B	◆	■	■
Anidulafungin	◆	◆	◆
Caspofungin	◆	◆	◆
Fluconazole	▲	◆	▲
Flucytosine	◆	■	■
Griseofulvin	■	◆	■
Itraconazole	■	■	■
Ketoconazole	■	■	■
Miconazole	◆	◆	◆
Nystatin	◆	◆	◆
Posaconazole	■	◆	■
Terbinafine	▲	◆	▲
Voriconazole	■	◆	■

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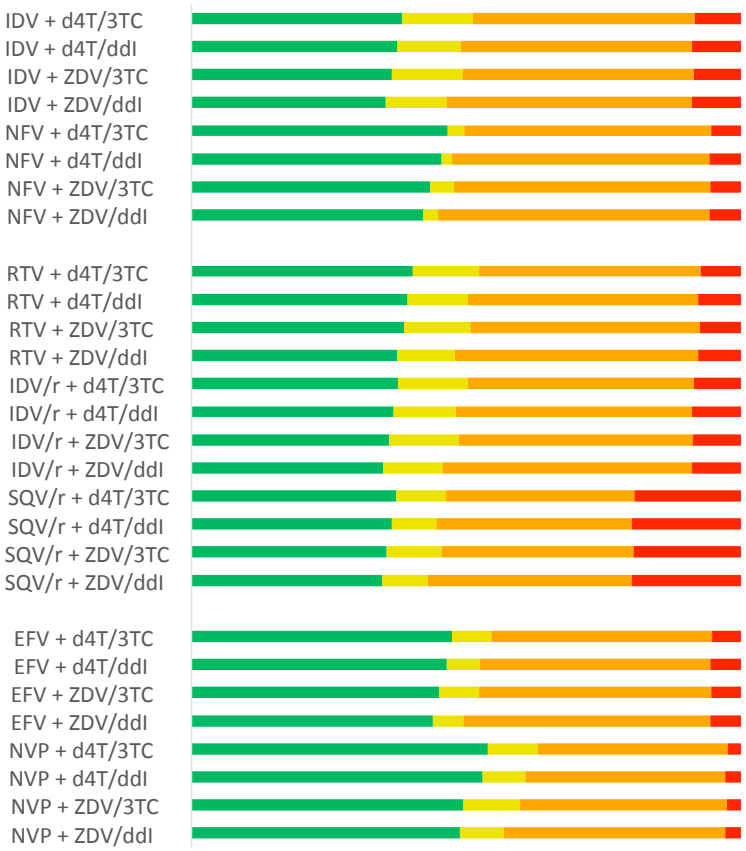
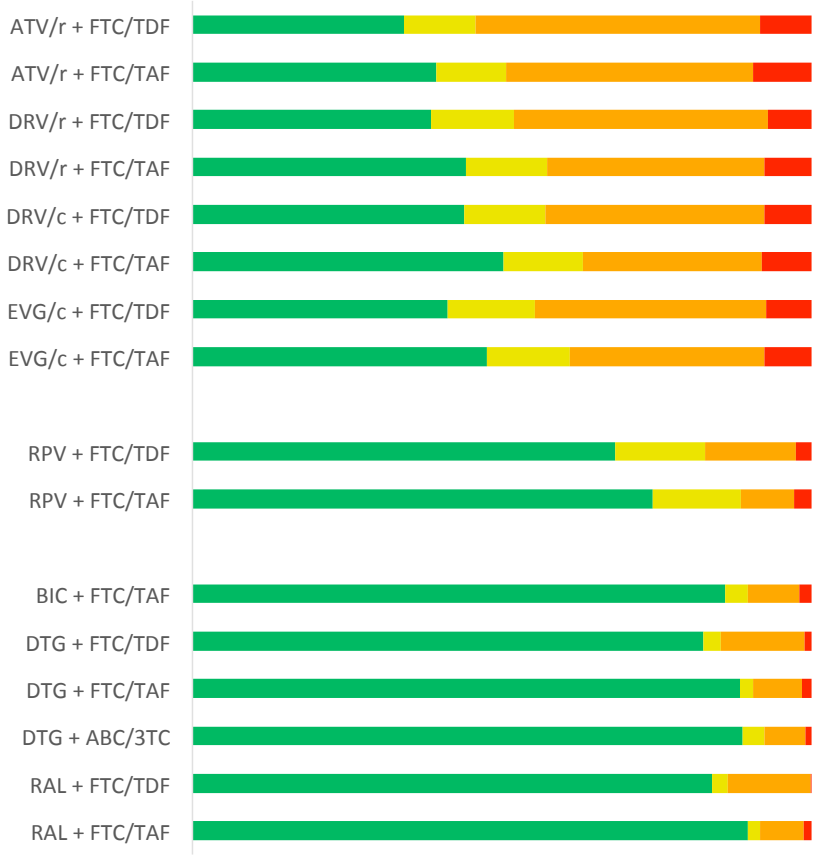
Interaction Profiles of First-line Regimens



Historic



Current

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Determination of "Interaction Potential"

- Interactions divided into two groups:
  - Intervention required (red and amber)
  - No a priori intervention required (green and yellow)
- "Interaction Potential" = % of red/amber interactions

	EVG/c/FTC/TDF
Amphotericin B	🟧
Anidulafungin	🟩
Caspofungin	🟩
Fluconazole	🟨
Flucytosine	🟧
Griseofulvin	🟧
Itraconazole	🟧
Ketoconazole	🟧
Miconazole	🟩
Nystatin	🟩
Posaconazole	🟧
Terbinafine	🟨
Voriconazole	🟧
Green/Yellow	6
Red/Amber	7
Interaction potential	54%

	DRV/c/FTC/TDF	DRV/c	FTC/TDF
Amphotericin B	🟧	🟩	🟧
Anidulafungin	🟩	🟩	🟩
Caspofungin	🟩	🟩	🟩
Fluconazole	🟨	🟨	🟩
Flucytosine	🟧	🟩	🟧
Griseofulvin	🟧	🟧	🟩
Itraconazole	🟧	🟧	🟧
Ketoconazole	🟧	🟧	🟧
Miconazole	🟩	🟩	🟩
Nystatin	🟩	🟩	🟩
Posaconazole	🟧	🟧	🟩
Terbinafine	🟨	🟨	🟩
Voriconazole	🟧	🟧	🟩
Green/Yellow	6	8	9
Red/Amber	7	5	4
Interaction potential	54%	38%	31%

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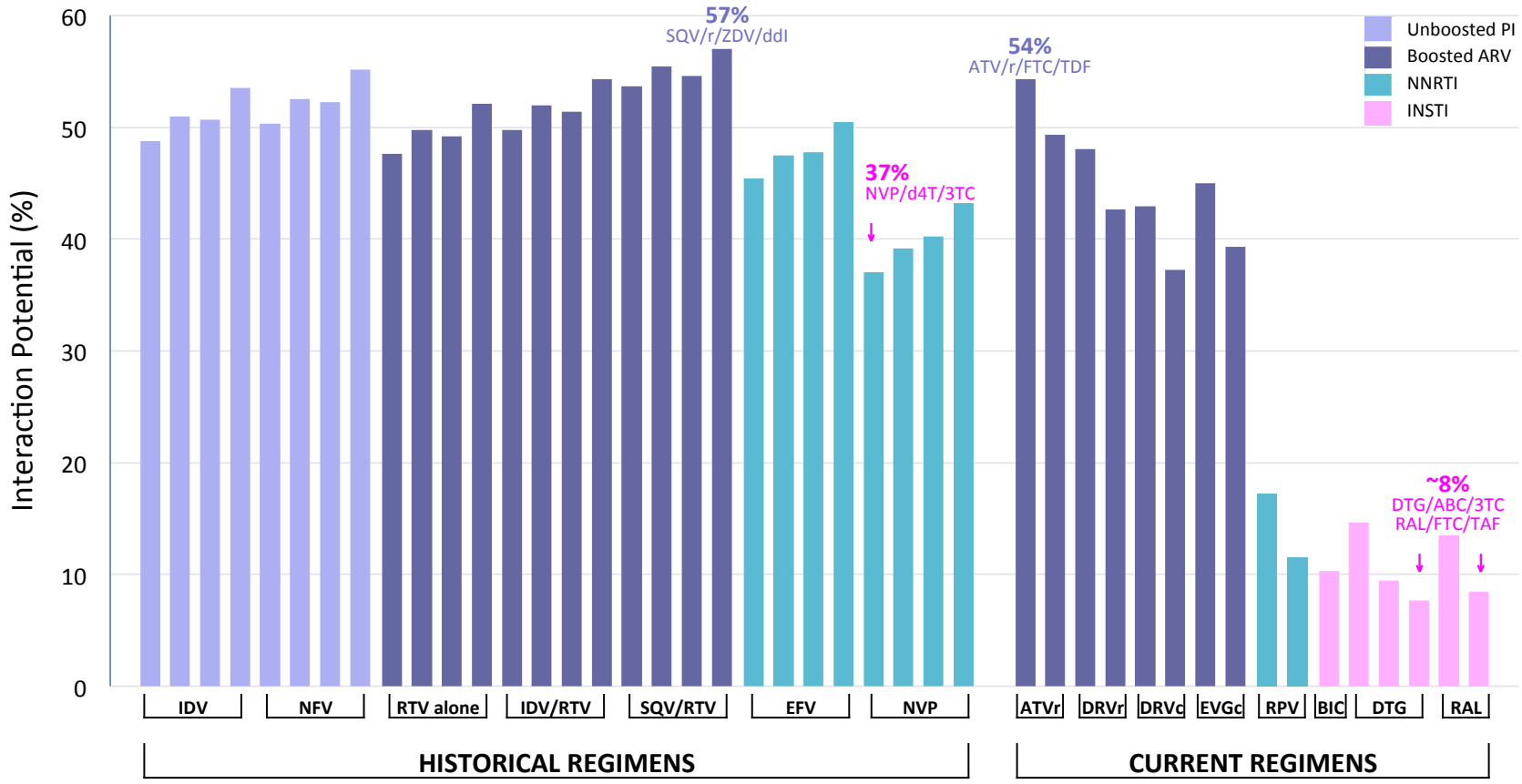
Interaction Potential – Effect of Drug/Class



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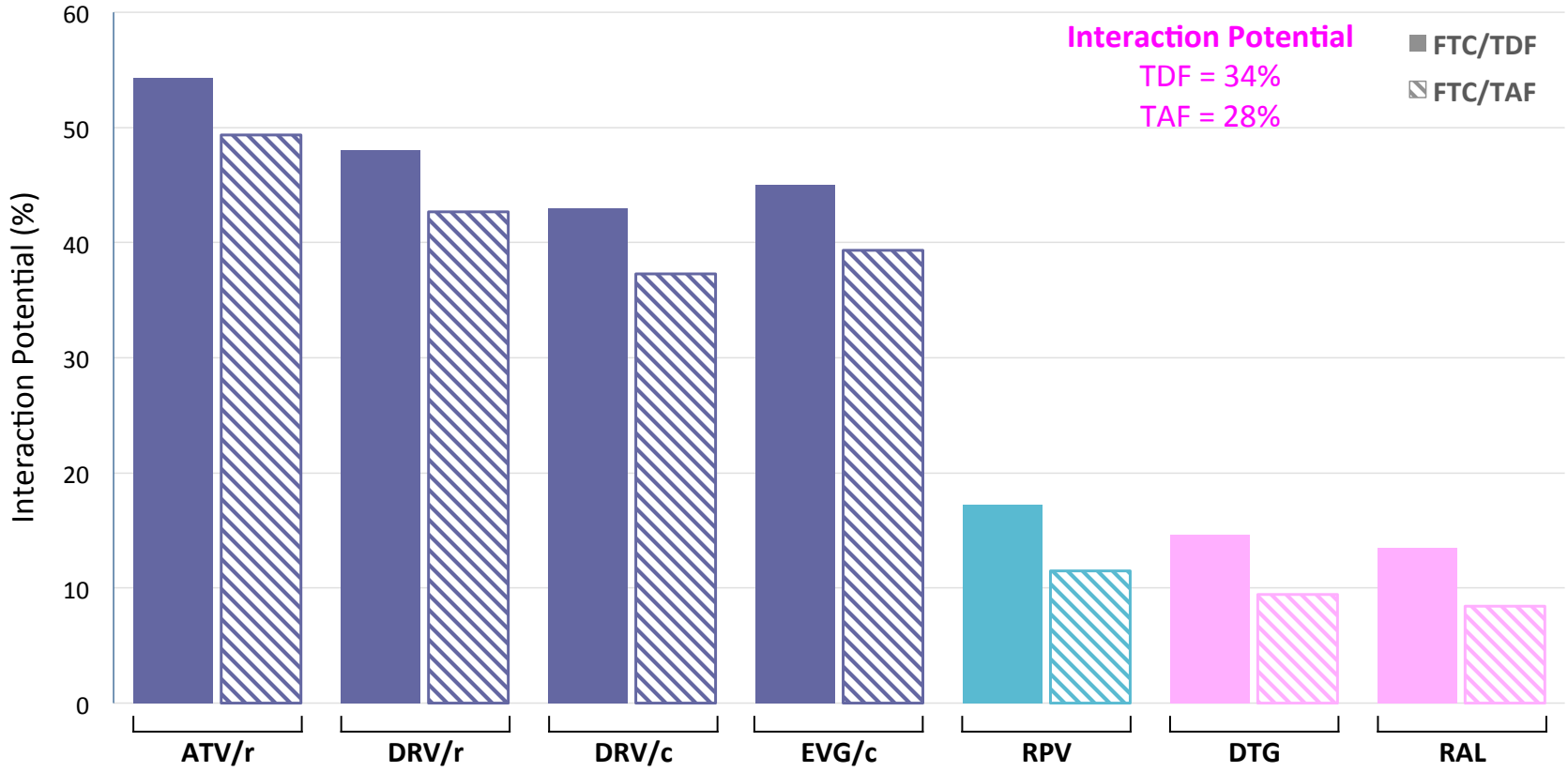
Interaction Potential – TDF vs TAF



Which of the 700+ comedications are likely to be used?

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Comorbidity Clusters

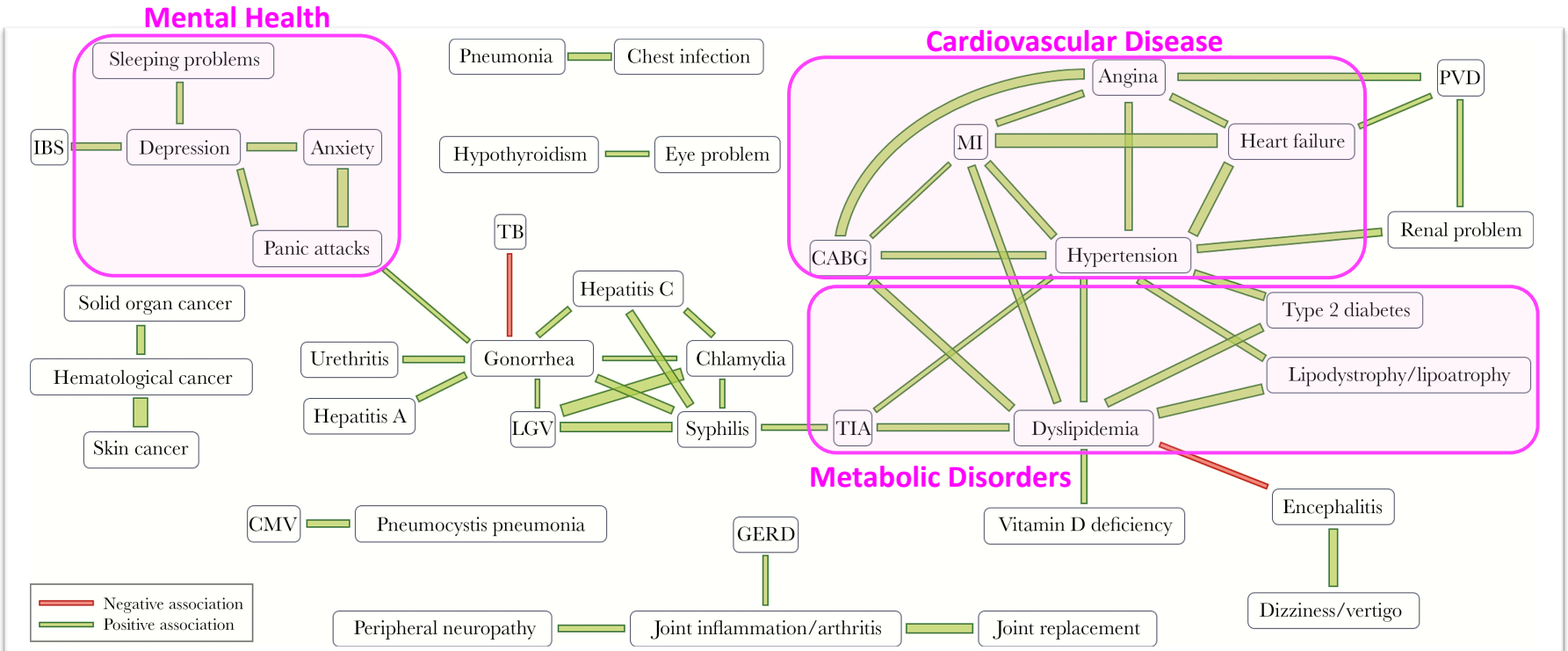

Figure 1. Significant non-random associations between comorbidities (as indicated by a significant Somers' D at the 0.1% significance level) in all POPPY PLWH (n = 1073). The thickness of the line is directly proportional to the absolute value of the Somers' D. Abbreviations: CABG, coronary artery bypass graft; CMV, cytomegalovirus; GERD, gastro-esophageal reflux disease; IBS, irritable bowel syndrome; LGV, lymphogranuloma venereum; MI, myocardial infarction; PLWH, people living with HIV; PVD, peripheral vascular disease; TB, tuberculosis; TIA, transient ischemic attack.

De Francesco D, et al. Open Forum Infect Dis. 2018 Oct 24;5(11):ofy272.

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Comorbidity Clusters - Comedications

	Mental Health	Cardiovascular Diseases	Metabolic Disorders
Drug Classes	Anxiolytics Hypnotics Sedatives Antidepressants	Beta blockers Calcium channel blockers Hypertensives Heart failure agents	Antidiabetic drugs Lipid lowering agents
Comedications	49	71	36

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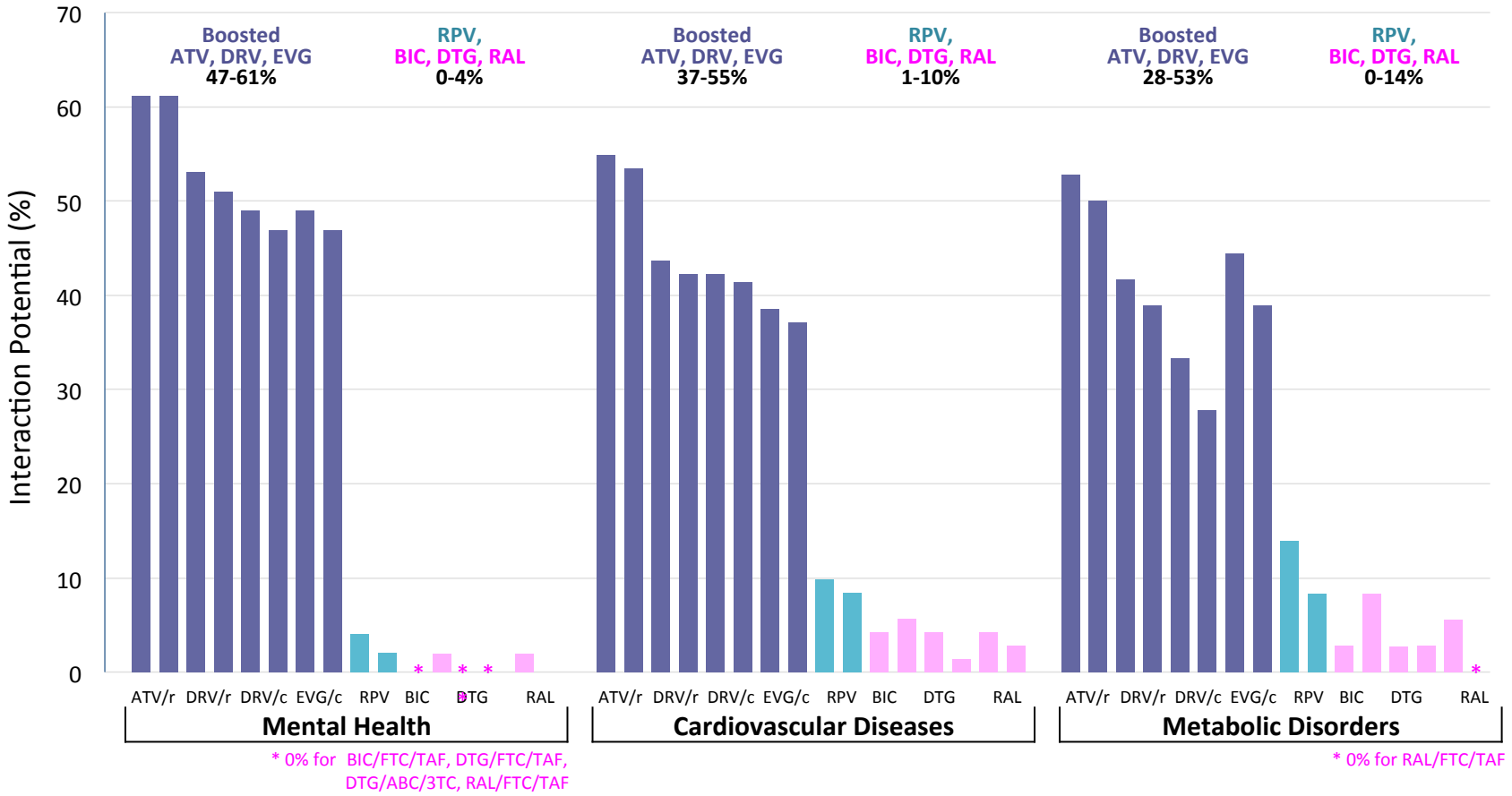
Comorbidity Clusters – Interaction Potential



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Conclusions

- A decline in interaction potential for first line therapies was observed, with the interaction potential of the least interacting regimen decreasing from 37% in 2000 to 8% for current regimens.
- The decline is due in part to new drugs within the same class (i.e., rilpivirine) or new classes (i.e., integrase inhibitors).
- The interaction potential of the nucleoside backbone is slightly lower for TAF-containing regimens (28%) than for TDF-containing regimens (34%).
- For treatment of comorbidities, the interaction potential ranged from 61% with ATV/r-containing regimens in the mental health cluster to 0% with some integrase-containing regimens in the mental health and metabolic disorder clusters.

1999 → 2019 = ↓ pill burden + ↓ interaction potential

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Acknowledgements