New antiretroviral therapies

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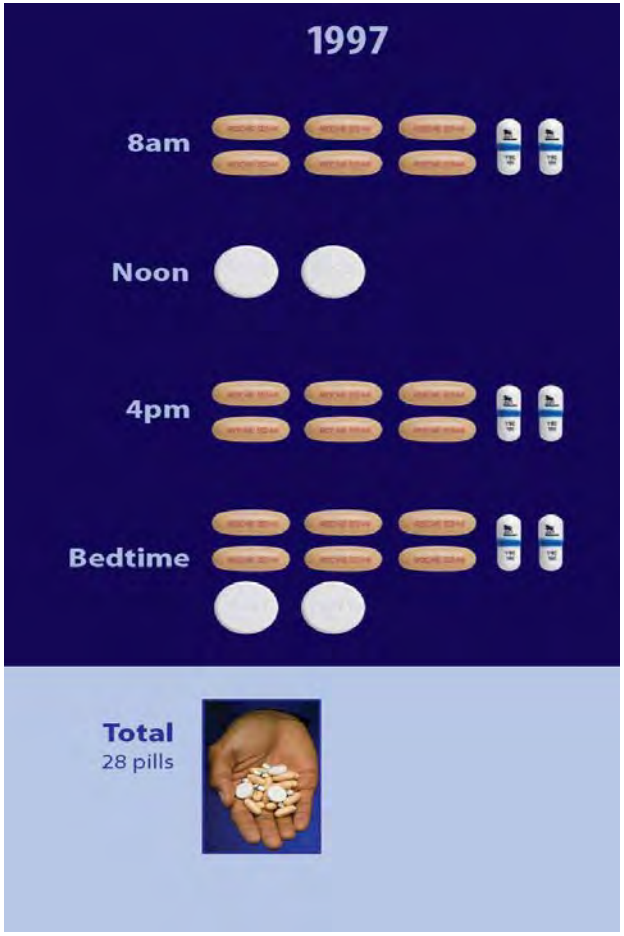
2012

25 drugs in 25 years

Antiretroviral Drugs

NRTI	NtRTI	NNRTIs	PIs	Fusion inhibitor	Co-receptor inhibitor	Integrase inhibitor
Zidovudine Lamivudine Stavudine Didanosine Abacavir Emtricitabine Zalcitabine	Tenofovir	Efavirenz Etravirine Nevirapine Rilpivirine Delavirdine	Lopinavir Atazanavir Ritonavir Darunavir Nelfinavir Saquinavir Indinavir Fosamprenavir Tipranavir Amprenavir	Enfuvirtide	Maraviroc Vicriviroc	Raltegravir Elvitegravir

Once daily dosing with one tablet



Atripla

- TDF / FTC/ EFV
- First line regimen
- Generics already available

SA HIVC Soc Guidelines (2008)

FIRST LINE

- NNRTIs and safe dual NRTI combinations

Recommended Dual NRTI's

- Emtricitabine + Tenofovir
- Lamivudine + Zidovudine
- Lamivudine + Abacavir

SECOND-LINE ART

The following ritonavir-boosted PIs are recommended in conjunction with 2NRTIs:

- atazanavir
- lopinavir
- saquinavir

Atazanavir

- Protease inhibitor
- Recommended dose
  - (boosted) 300mg /100mg
  - (unboosted) 400mg
- Common Adverse effects
  - Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus
  - Nephrolithiasis
  - Skin rash
  - Food requirement
  - Absorption depends on food and low gastric pH
- Unboosted ATV cannot be coadministered with TDF, EFV, or NVP

Atazanavir

- Benefits
  - Fewer adverse effects on lipids than other PIs
  - Once-daily dosing
  - Low pill burden
  - Good GI tolerability
  - Signature mutation (I50L) not associated with broad PI cross resistance

Newly registered ARVs

- Darunavir (Prezista®)

  Registered in August 2010

  *PREZISTA, in combination with 100 mg ritonavir (PREZISTA/rtv) and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral **treatment experienced** adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.*

- Raltegravir (Isentress®)

  Registered in March 2011

  *ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in **treatment-experienced** adult patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy.*

- Etravirine (Intelence®)

  Registered in Nov 2011

  *INTELENCE, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral **treatment-experienced** adult patients with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance.*

Darunavir

- The ARTEMIS study compared DRV/r (800/100 mg once daily) with LPV/r(once or twice daily), both in combination with TDF/FTC, in a randomized, open-label, non inferiority trial. The study enrolled 689 **ART-naive** participants.
- At 48 weeks, DRV/r was noninferior to LPV/r. Among those participants whose baseline HIV RNA levels were >100,000 copies/mL, the virologic response rates were lower in the LPV/r arm than in the DRV/r arm.
- Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in LPV/r recipients than in DRV/r .
- 96 weeks, virologic response to DRV/r was superior to response to LPV/r.

TITAN trial

- 594 patients from 26 countries, were randomised to optimum background therapy (OBT) plus either DRV/r or LPV/r, both at standard twice-daily dosing.
- Patients needed to be on failing therapy that did not contain LPV/r, with viral load >1,000 copies/mL
- At 48 weeks, a significantly greater proportion of patients achieved undetectable viral load: <400 copies/mL (77% vs 67%, p=0.008) and <50 copies/mL (71% vs 60%, p=0.005), in the DRV/r vs LPV/r arms respectively, with mean changes in viral load of -1.95 (+/-1.24) and -1.72 (+/-1.34) log (p=0.046).
- The results by baseline sensitivity indicate that while lopinavir/r will not rescue patients with loss of sensitivity to darunavir/r, darunavir is certainly more active than lopinavir in patients with loss of sensitivity to lopinavir

Darunavir

- 24-week data, randomized phase IIb trials, TMC114-C213 and TMC114-C202 (POWER 1 and POWER 2 trials)
- HIV-1 infected subjects who were eligible for these trials had :
  - plasma HIV-1 RNA > 1000 copies/mL,
  - had prior treatment with PI(s), NNRTI(s) and NRTI(s),
  - had at least one primary PI mutation (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening,
  - and were on a stable PI-containing regimen at screening for at least 8 weeks
  - Analyses included 318 subjects in Study TMC114-C213 and 319 subjects in Study TMC114-C202 who had completed 24 weeks of treatment or discontinued earlier.

Darunavir (Prezista®)

- Through 24 weeks of treatment, the proportion of subjects with HIV-1 RNA < 400 copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. compared to the comparator PI arm was 63% and 19%, respectively

- In addition, the mean changes in plasma HIV-1 RNA from baseline were -1.89 $\log_{10}$ copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. and -0.48 $\log_{10}$ copies/mL for the comparator PI arm.

- The mean increase from baseline in CD4+ cell counts was higher in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. (92 cells/mm^3) than in the comparator PI arm (17 cells/mm^3).

Table 8: Outcomes of Randomized Treatment Through Week 24 of the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)		
	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600 mg b.i.d. + OBR N=131	Comparator PI + OBR N=124
Virologic Responders confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline through Week 24 (< 50 copies/mL at Week 24)	69.5% (45.0%)	21.0% (12.1%)
Virologic failures	26.0%	71.0%
Lack of initial response^	9.9%	57.3%
Rebound†	9.2%	9.7%
Never Suppressed‡	6.9%	4.0%
Death or discontinuation due to adverse events	3.9%	1.6%
Discontinuation due to other reasons	0.8%	6.5%

^ Subjects who did not achieve at least a confirmed 0.5 $\log_{10}$ HIV-1 RNA drop from baseline at Week 12

† Subjects with an initial response (confirmed 1 $\log_{10}$ drop in viral load), but without a confirmed 1 $\log_{10}$ drop in viral load at Week 24

‡Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 24

Recommended dose

- *Adults:* The recommended oral dose of PREZISTA tablets is 600 mg (two 300 mg tablets) twice daily taken with ritonavir 100 mg twice daily and with food. The type of food does not affect exposure to darunavir.

- *Renal Impairment:* No dose adjustment is required in patients with moderate renal impairment.

Table 12: Percentage of Subjects with Selected Treatment Emergent, Drug-Related^ Adverse Events of at least Moderate Intensity (Grades 2-4) in ≥ 2% of Adult Subjects in Any PREZISTA/rtv Treatment Groups†

System Organ Class, Preferred Term, %	Randomized Studies TMC114-C213 and TMC114-C202		Non-randomized TMC114-C215/C208 Analysis
	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 131	Comparator PI +OBR N = 124	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 327
Gastrointestinal Disorders			
Diarrhea	2.3%	3.2%	2.8%
Vomiting	1.5%	1.6%	2.4%
Abdominal Pain	2.3%	0.8%	1.2%
Constipation	2.3%	0.8%	0.6%
Nervous System Disorders			
Headache	3.8%	2.4%	0.9%

^ Includes adverse events at least possibly, probably, or very likely related to the drug
N=total number of subjects per treatment group
† Excludes laboratory abnormalities that were reported as Adverse Events (see Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥ 2% of Subjects)

Side Effects

- Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythremamultiforme have been reported.
- • Hepatotoxicity
- • Diarrhea, nausea
- • Headache
- • Hyperlipidemia
- • Serum transaminase elevation
- • Hyperglycemia
- • Fat maldistribution

Drug Interactions

- Darunavir and ritonavir are both inhibitors of the CYP3A4 isoform.
- DRV/r ↓ S-warfarin AUC 21%
- DRV/r ↑ clarithromycin AUC 57%
- DRV/r rosuvastatin AUC ↑ 48% and Cmax ↑ 139%
- DRV/rtv should not be used in combination with rifampicin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA

Resistance to Darunavir

- Darunavir has a high genetic barrier to the development of resistance and did not display cross-resistance with other PIs *in vitro*
- Although no single mutation has been found to confer high-level resistance to darunavir, resistance mutations selected by other protease inhibitors can contribute to darunavir resistance.
- A number of protease mutations, including V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V, are associated with decreased virologic response to darunavir, particularly in ≥2 of these are present.
- The total number of primary protease mutations (as defined by the International AIDS Society-USA [IAS-USA]) is associated with diminished response to darunavir.
- If 7 or more protease resistance mutations are present at baseline, the probability of darunavir + ritonavir treatment failure increases significantly.

Raltegravir (Isentress®)

Integrase Strand Transfer Inhibitor (INSTI)

- Inhibition of proviral HIV DNA integration (a multi-step process)into host genome
- Raltegravir inhibits the strand transfer step
- New class

Raltegravir Clinical Trials

- The STARTMRK Study – Naïve patients
- The BENCHMRK Study -
- The SWITCH-ER Study
- The SPIRAL Study
- The REALMRK Study

The STARTMRK study

- The STARTMRK(Safety and Efficacy of Raltegravir-Based versus Efavirenz-Based Combination Therapy in Treatment-Naïve HIV-1 Infected Patients) study evaluated raltegravir 400mg twice a day versus efavirenz 600mg at bedtime with tenofovir/emtricitabine in treatment-naive patients.

- There were no significant differences between raltegravir and efavirenz in the percentage of patients achieving an undetectable HIV viral load, although the increase in absolute CD4+ cell count with raltegravir was greater than with efavirenz

- Raltegravir 400 mg twice daily provided a rapid and durable improvement in virological outcomes, which was statistically noninferior to oral efavirenz 600 mg once daily at both weeks 48 and 96, in the ongoing STARTMRK trial.

- Lipid profiles were less affected with raltegravir than with efavirenz

The BENCHMRK Study

- The BENCHMRK (Blocking Integrase in Treatment-Experienced Patients with a Novel Compound Against HIV) 1 and 2 studies compared raltegravir plus OBR with placebo plus OBR in ART-experienced patients who had antiretroviral resistance
- After 48 weeks, patients in the raltegravir arms were significantly more likely to achieve an undetectable viral load compared with those in the placebo arm. The best virological result occurred in those patients who received raltegravir with both darunavir and enfuvirtide in their OBR (89%).
- Remarkably,50% of those receiving raltegravir with no other active drugs in the OBR achieved an undetectable viral load compared with only 2% of patients receiving placebo plus OBR.
- The BENCHMRK and other trials led to the approval of raltegravir for treatment-experienced HIV-1 infected adults with detectable viral loads and resistance to multiple antiretroviral drugs.

The SWITCH-ER Study

- Patients who tolerated EFV, with less than 50 copies/ml HIV-RNA, were randomized into two groups:
  - the RAL-first group started with RAL (400mg twice daily) and EFV placebo, and the EFV first group with EFV (600mg once daily) and RAL placebo.
  - After 2 weeks, both group switched to the alternate regimen. The primary endpoint was patient preference for thefirst or the second regimen, assessed after 4 weeks.
- Fifty seven participants were enrolled with a median CD4 cell count 600/ml,and duration of previous EFV therapy 3.4 years.
- Fifty three participants completed the study.
- Half of patients previously on a stable EFV preferred to switch to RAL, after double-blind exposure to RAL for 2 weeks.
- Substitution of EFV by RAL significantly impacted on lipid levels, stress, and anxiety scores (P = 0.036, 0.04 and 0.03 respectively)

The SPIRAL Study

- A 48-week multicentre, open-label trial in which HIV-infected adults with less than 50 copies/ml of plasma HIV RNA for at least the previous 6 months on ritonavir-boosted protease inhibitor-based therapy were randomized (1 : 1) to switch from the ritonavir-boosted protease inhibitor to raltegravir or to continue on ritonavir boosted protease inhibitor-based therapy.
- 273 patients assigned to switch to raltegravir (n=139) or to continue ritonavir-boosted protease inhibitor (n=134) were included in the efficacy analysis.
- At 48 weeks, 89.2% (raltegravir-based therapy) and 86.6% (ritonavir-boosted protease inhibitor-based therapy) of the patients remained free of treatment failure [difference 2.6%; 95% confidence interval (CI)5.2 to 10.6].
- In patients with sustained virological suppression on ritonavir-boosted protease inhibitor-based therapy, switching from ritonavir-boosted protease inhibitor to raltegravir demonstrated noninferior efficacy and resulted in a better lipid profile at 48weeks than continuing ritonavir-boosted protease inhibitor

The REALMRK Study

- Multicenter, open-label, single-arm study
- Conducted in North America (USA), South America (Brazil, Dominican Republic, Jamaica) and Southern Africa (South Africa)
- Raltegravir 400 mg given BID for up to 48 weeks in combination with additional ART, selected at baseline & limited to approved and licensed agents
- Categories of treatment experience
  - Treatment-experienced, failing current therapy
  - Treatment-experienced, intolerant to current therapy
  - Treatment-naïve (limited to ≤20% of total*)
- Enrollment targets
  - at least 25% female
  - at least 50% African-American (US black patients)

The REALMRK Study

- After 48 weeks of treatment in a very diverse cohort of HIV-infected patients
  - Raltegravir 400 mg BID had potent efficacy regardless of gender or race
  - Raltegravir 400 mg BID was generally safe and well tolerated
  - Overall, 15% of patients discontinued: 17% of women vs 13% of men; 14% of black patients vs 17% of non-black patients
  - Raltegravir PK parameters calculated from sparse sampling were consistent with expectations based on prior studies of raltegravir 400 mg BID; there was no significant effect of gender or race (black vs non-black) on PK

Raltegravir

- It is metabolized primarily by glucuronidation (UGT1A1) and is not a potent inhibitor or inducer of CYP3A4
- It displays distinct viral dynamics compared with other ARTs, with a more rapid onset of action and a greater reduction in second-phase viraemia.
- Rapid absorption
- RAL requires twice-daily dosing,has a low genetic barrier for selection of resistance mutations, and has had relatively limited use with otherdual-NRTI combinations.

Raltegravir

ADVANTAGES

- Virologic response non-inferior to EFV
- Fewer drug-related adverse events and lipid changes than EFV
- No food effect
- Fewer drug-drug interactions than PI- or NNRTI-based regimens

Raltegravir

DISADVANTAGES

- Twice-daily dosing
- Lower genetic barrier to resistance than with boosted PI based regimens
- No data with NRTIs other than TDF/FTC in ART-naive patients
- Increase in creatine kinase, myopathy, and rhabdomyolysis have been reported
- Rare cases of severe skin reactions (including SJS and TEN) have been reported and systemic HSRs with rash and constitutional symptoms, with or without hepatitis, have been reported.

Raltegravir (Isentress®)	
Route of administration	Oral
Dose	400mg
Frequency of administration	Twice daily (with or without food)
Most frequent moderate-to-severe treatment-related adverse events (incidence >2%)	Headache, insomnia and nausea

Raltegravir

- Sex, race, moderate hepatic impairment and severe renal impairment had no clinically significant effect on the pharmacokinetic profile of raltegravir; consequently, dosage adjustments are not necessary in these patient subgroups.

- Raltegravir is not approved in paediatric patients

Resistance to Raltegravir

- Complete loss of antiviral activity can occur with single mutations.
- Pathways to raltegravir resistance usually involve Y143R/C, Q148K/R/H or N155H, alone or in combination with other mutations such as G140S.
- N155H and Q148R/H/K have been identified as 'signature' resistance mutations in patients failing both raltegravir and elvitegravir, whereas Y143R/C was mainly associated with raltegravir, and E92Q and S147G were mainly associated with elvitegravir. Other resistance integrase mutations were observed in patients failing raltegravir and/or elvitegravir (L74M, T97A, E138K,G140SAC, and G163R). However, they had little or no effect on drug susceptibility in vitro in the absence of a primary 'signature' mutation, thus suggesting rather a secondary role for viral fitness rescue and/or increasing resistance

Etravirine (Intelence®)

- Second generation NNRTI
- Received approval on the basis of a pooled analysis of DUET 1 & DUET 2

DUET1 & DUET 2

- DUET-1 and DUET-2 Phase III trials demonstrated the efficacy and safety of etravirine (ETR; TMC125) in treatment-experienced patients.

- Treatment-experienced patients with documented NNRTI resistance, ≥3 primary protease inhibitor (PI) mutations and viral load >5000 copies/mL were randomized 1:1 to receive ETR 200mg or placebo bid plus background regimen (BR; darunavir with low-dose ritonavir [DRV/r], optimized NRTI[s] ± enfuvirtide [ENF]). The primary endpoint was the percentage of patients with confirmed viral load <50 copies/mL (intent-to-treat [ITT] population; time-to-loss of virologic response [TLOVR] algorithm).

DUET 1 & DUET 2

- ETR + BR demonstrated superior virologic responses than placebo + BR in treatment-experienced patients at 48 weeks– 61% of patients in the ETR group achieved confirmed undetectable viral load (<50 copies/mL) compared with 40% in the placebo group.
- When analyzed by selected baseline characteristics, patients in the ETR group consistently achieved higher response rates than those in the placebo group, irrespective of ENF use, race, disease characteristics, or previous NNRTI use.
- Baseline viral load, CD4 cell count, ENF use and number of sensitive background ARVs were predictors of response in both treatment groups; nevertheless ETR provided added benefit in each subgroup

Etravirine

- ETR at a dose of 200 mg twice daily is approved for use in treatment-experienced patients with virologic failure.
- In a small, randomized, double-blind, placebo-controlled trial, ETR 400 mg once daily was compared with EFV 600 mg once daily (both in combination with two NRTIs) in treatment-naive subjects. Seventy-nine and 78 participants were randomized to the ETR and EFV arms, respectively.
- At 48 weeks,76% of the ETR recipients and 74% of the EFV recipients achieved plasma HIV RNA <50 copies/mL.
- Neuropsychiatric side effects were more frequently reported in the EFV recipients than in the ETRrecipients.
- These results suggest that once-daily ETR may be a potential NNRTI option in treatment-naivepatients. However, more data are required and, pending results from larger trials.

Etravirine

- Dosage
  - 200mg twice daily orally
- Should be taken with a meal
- Dosage adjustments are not required in patients with renal impairment or mild to moderate hepatic impairment
- Side effects
  - Rash including SJS
  - HSRs
  - Nausea

Etravirine drug interactions

- ETR is an inducer of CYP3A4 and UDPGT and an inhibitor of CYP2C9 and

  CYP2C19.
- ETR clarithromycin AUC ↓ 39% ETR AUC ↑ 42% Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
- Rifabutin
  - Exposure to ETR may be altered (AUC12 Cmax ↓ by 37%)[43]
- Rifampicin (rifampin)
  - ↓ ETR plasma concentrations

Resistance to Etravirine

- Etravirine is a second-generation NNRTI with a higher genetic barrier to resistance than nevirapine or efavirenz.
- There are 17 etravirine RAMs (V90I, A98G,LI001, KIOIE/H/P, VI061, EI38A, V179D/F/T, Y181C/I/V, G190A/S and M230L) and their effects are most significant when three or more are present. However, individual mutations have different impacts on viral susceptibility to etravirine, with Y181I, Y181V, K1O1P, L1OO1,Y181C and M230L having the highest impact; thus, fewer than three mutations may confer resistance in some cases.
- K103N has no effect on etravirine susceptibility

Combination of RAL/ETV/ DRV/Rt

- In the ANRS139-TRIO study, the combination of darunavir-ritonavir, etravirine and raltegravir showed efficacy in treatment-experienced patients.
- Ninety percent of patients achieved HIVRNA <50copies/mL at week 24 and 86% had plasma HIV RNA <50copies/mL at week 48.
- Other studies have shown similar effects of these three novel drugs

Yazdanpanah Y, Fagard C, Deseamps D, et al. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV; results of the ANRS 139 TRIO trial. Clin Infect Dis 2009; 49; 1444-9

Imaz A, del Saz SV, Ribas MA, et al. Raltegravir, etravirine and ritonavir-boosted darunavir; a safe and successful rescue for multidrug-resistant HIV-infection. J Acquir Immune Defic Syndr 2009; 52 (3); 382-6

Thuret I, Chaix M, Tamalet C, et al. Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. AIDS 2009; 23 (17); 2364-6

American Guidelines (1st line regimens)

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use)

The preferred regimens for non-pregnant patients are arranged by chronological order of FDA approval of components other than nucleosides and, thus, by duration of clinical experience.

NNRTI-Based Regimen

- EFV/TDF/FTC[a] **(AI)**

PI-Based Regimens (in alphabetical order)

- ATV/r + TDF/FTC[a] **(AI)**
- DRV/r (once daily) + TDF/FTC[a] **(AI)**

INSTI-Based Regimen

- RAL + TDF/FTC[a] **(AI)**

Preferred Regimen for Pregnant Women[b]

- LPV/r (twice daily) + ZDV/3TC[a] **(AI)**

Comments

EFV should not be used during the first trimester of pregnancy or in women of childbearing potential who are trying to conceive or not using effective and consistent contraception.

TDF should be used with caution in patients with renal insufficiency.

ATV/r should not be used in patients who require >20 mg omeprazole equivalent per day. Refer to Table 15a for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.

American Guidelines (1st Line Regimens)

Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)

NNRTI-Based Regimens (in alphabetical order) • EFV + ABC/3TC[a] **(BI)** • RPV/TDF/FTC[a] **(BI)** • RPV + ABC/3TC[a] **(BIII)** *PI-Based Regimens (in alphabetical order)* • ATV/r + ABC/3TC[a] **(BI)** • DRV/r + ABC/3TC[a] **(BIII)** • FPV/r (once or twice daily) + ABC/3TC[a] or TDF/FTC[a] **(BI)** • LPV/r (once or twice daily) + ABC/3TC[a] or TDF/FTC[a] **(BI)** *INSTI-Based Regimen* • RAL + ABC/3TC[a] **(BIII)**	*Comments* • Use **RPV** with caution in patients with pretreatment HIV RNA >100,000 copies/mL. • Use of PPIs with **RPV** is contraindicated. • **ABC** should not be used in patients who test positive for HLA-B*5701. • Use **ABC** with caution in patients with known high risk of CVD or with pretreatment HIV RNA >100,000 copies/mL. (See text.) **Once-daily LPV/r** is not recommended for use in pregnant women.

European Guidelines (1st line regimens)

	PREFERRED	ALTERNATIVE
NRTI backbone	**Tenofovir + emtricitabine**	**Abacavir[1,3] + lamivudine [(2)]**
Third Agent	**Atazanavir/ritonavir** **Darunavir/ritonavir** **Efavirenz** **Raltegravir**	**Lopinavir/ritonavir[3]** **Fosamprenavir/ritonavir[3]** **Nevirapine[4]** **Rilpivirine[2]**

1. Contraindicated if HLA B*5701 positive
2. Not recommended if baseline viral load greater than 100,000 copies/ml
3. Not recommended if high estimated cardiovascular risk (see Section 6.6 Cardiovascular disease)
4. Contra-indicated if baseline CD4 greater than 250/400 cells/µL in women/men.

Regimen selection

- comorbid conditions (e.g., cardiovascular disease [CVD], chemical dependency, liver disease, psychiatric disease, renal diseases, or tuberculosis [TB]);
- potential adverse drug effects;
- potential drug interactions with other medications;
- pregnancy or pregnancy potential;
- result of genotypic drug-resistance testing;
- gender and pretreatment CD4 count if considering nevirapine (NVP);
- coreceptor tropism assay if considering maraviroc (MVC);
- patient adherence potential; and
- convenience (e.g., pill burden, dosing frequency, and food and fluid considerations).

Product Name	Active	Pack Size	Wholesale price incl VAT
Isentress	Raltegravir	60	897.17
Intelence	Etravirine	120	832.05
Prezista	Darunavir	120	738.86

NNRTI based regimens

- Class advantages
  - Long half-lives
- Class disadvantages
  - Greater risk of resistance at the time of treatment failure with NNRTIs than with PIs
  - Potential for cross resistance
  - Skin rash
  - Potential for CYP450 drug interactions
  - Transmitted resistance more common with NNRTIs than with PIs

Protease inhibitor based regimens

- RTV-boosted PI-based regimens have shown good virologic and immunologic responses but are often associated with more gastrointestinal (GI) symptoms than EFV-based regimens
- Drug resistance to most PIs requires multiple mutations in the HIV protease gene and seldom develops after early virologic failure,
- Most PI-based regimens include RTV, may be dosed once or twice daily, and have a higher pill burden than NNRTI regimens
- Clinically significant interactions are seen with RTV-boosted PI regimens than with NNRTI-based regimens.

Maraviroc

- Prevent HIV entry into target cells by binding to the CCR5 receptor
- The vast majority of patients harbor a CCR5-utilizing virus (R5 virus) during acute/recent infection

Maraviroc

ADVANTAGES

- Virologic response non inferiorto EFV in post hoc analysis of MERIT study
- Fewer adverse effects than EFV

DISADVANTAGES

- Requires viral tropism testing prior to initiation of therapy, which results in additional cost and possible delay in initiation of therapy
- More MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy in **MERIT** study
- Less long-term experience in ART-naive patients than with boosted PI- or NNRTI-based regimen
- Limited experience with dual-NRTIs other than ZDV/3TC
- Twice-daily dosing
- CYP 3A4 substrate; dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s)

Rilpivirine

- Once-daily dosing
- Coformulated with TDF/FTC
- Compared with EFV:
  - Fewer discontinuations for CNS adverse effects
  - Fewer lipid effects
  - Fewer rashes

- More virologic failures in patients with pretreatment HIV RNA>100,000 copies/mL than with EFV-based regimen
- More NNRTI- and 3TC-associated mutations at virological failure than with regimen containing EFV + two NRTI

Rilpivirine

- Food requirement
- Absorption depends on lower gastric pH
- Contraindicated with PPIs
- RPV-associated depression reported
- Use RPV with caution when coadministered with a drug having aknown risk of torsades de pointes.

Rilpivirine

- Three mutations have been identified as being associated with decreased susceptibility to rilpivirine in vitro (K101P, Y181I and Y181 V) and the resistance profile of rilpivirine appears to be more robust than those of first-generation NNRTIs [13]. Thus, rilpivirine may represent a viable future NNRTI treatment option for ART-naive patients and, like the second-generation NNRTI etravirine, may potentially have use in the treatment of HIV-infected patients with resistance to other NNRTIs, although its use in this setting has yet to be evaluated.

Thank you