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What's New in Antiretroviral Therapy

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Current guidelines recommend non-nucleoside reverse transcriptase inhibitor (NNRTI)-based, boosted protease inhibitor (PI)-based, and integrase strand transfer inhibitor (INSTI)-based regimens for the treatment of HIV [http://aidsinfo.nih.gov/Guidelines/HTML/1/adult-and-adolescent-treatment-guidelines/0; Thompson MA et al. *JAMA* 2012]. Joel E. Gallant, MD, MPH, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, discussed recent data from clinical trials comparing initial antiretroviral regimens and factors to be considered when starting antiretroviral therapy (ART).

The ECHO and THRIVE trials were similar studies that compared the NNRTIs rilpivirine (RPV) and efavirenz (EFV) in antiretroviral-naïve HIV-1-infected adults. In a pooled analysis of data from these trials, viral suppression with RPV (25 mg QD) and EFV (600 mg QD) was comparable at Week 96 (78% in each arm). RPV was associated with more virologic failures but fewer discontinuations due to adverse events than EFV [Cohen CJ et al. IAS 2011 Poster TULBPE032].

Raltegravir (RAL) is an INSTI that has been compared with EFV in treatment-naïve patients. STARTMRK was a 5-year Phase 3 trial that reported noninferiority for RAL at 48 and 96 weeks, and superiority (71.0% vs 61.3% at Week 240 in patients with viral load <50 copies/mL; difference 9.5; 95% CI, 1.7 to 17.3; p<0.001) at 4 and 5 years of follow-up, largely driven by higher side effect-related discontinuations in the EFV arm [Rockstroh J et al. IAC 2012 Abstract LBPE19]. Virologic suppression is more rapid with RAL—an observation of uncertain clinical significance. As with NNRTIs, resistance is more likely to emerge with treatment failure of RAL than with ritonavir-boosted PI (PI/r)-based regimens.

The INSTI elvitegravir (EVG) has been coformulated with the pharmacoenhancer cobicistat (COBI), emtricitabine (FTC), and tenofovir DF (TDF) in a single once-daily tablet, sometimes referred to as the *quad*. In a pooled analysis of two Phase 3 and one Phase 2 randomized controlled trials, the quad demonstrated high rates of virologic suppression when compared with EFV/FTC/TDF and atazanavir/ritonavir (ATV/r) plus FTC/TDF with a slightly improved adverse event profile. Due to COBI's inhibition of renal creatinine tubular secretion, there were small increases in creatinine observed early in therapy with the quad; however, these stabilized through Week 48 [Ward D et al. ICAAC 2012 Abstract H-555]. In terms of resistance, failure on the quad can result in integrase mutations, while failure on EFV/FTC/TDF can lead to NNRTI mutations [Sax P et al. *Lancet* 2012]; those failing ATV/r plus FTC/TDF did not develop mutations [DeJesus E et al. *Lancet* 2012].

With respect to PIs, Dr. Gallant noted that the 800-mg tablet of darunavir is coming soon, as are DRV/COBI and ATV/COBI coformulations. In the future, a single-tablet PI formulation (DRV/COBI/GS7340/COBI) is expected.

Regarding nucleoside reverse transcriptase inhibitors (NRTIs), there have been some changes in the recommendations for abacavir (ABC). The combination of ABC and lamivudine (3TC) is now a recommended NRTI backbone in the IAS-USA guidelines for patients with negative HLA B*5701 assays and baseline viral loads <100,000 copies/mL; it remains an alternative backbone in the United States Department of Health and Human Services guidelines. AIDS Clinical Trials Group Study A5202 found a greater difference in efficacy based on pretreatment CD4 count and viral load with ABC/3TC compared with FTC/TDF [Grant P et al. CROI 2011 Abstract 535]. Adding to this concern have been conflicting reports concerning the risk of myocardial infarction with ABC. Dr. Gallant noted that TDF is not without risks, particularly kidney disease [Scherzer R et al. *AIDS* 2012] and a greater reduction in bone density than is seen with other agents, with a possible association with increased risk of bone fracture [Bedimo R et al. *AIDS* 2012]. He closed his presentation with a review of single-tablet regimens (Table 1).

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Table 1. Single-Tablet Regimens.

Regimen	Pros	Cons
TDF/FTC/EFV (Atripla)	• PK forgiving of missed doses • Long-term efficacy well established at all viral load and CD4 count strata	• CNS side effects • Teratogenicity • Risk of resistance with failure • Rash • Lipid effects • (short- and long-term)
TDF/FTC/RPV (Complera)	• Noninferior to TDF/FTC/EFV • Better tolerated than TDF/FTC/EFV	• Less effective than EFV at high viral loads • Less forgiving of nonadherence • More resistance with failure, including ETR cross-resistance • Meal requirement • No PPI, caution with H_2 blockers
TDF/FTC/EVG/COBI (Stribild)	• Noninferior to TDF/FTC/EFV • Better tolerated than TDF/FTC/EFV	• COBI drug interactions • COBI effect on eGFR • Meal requirement
ABC/3TC/DTG (coming soon)	• Only non–TDF-based STR • Superior to TDF/FTC/EFV due to better tolerability	• Possible association between ABC and risk of MI • Need for prescreening with HLA B*5701

3TC=lamivudine; ABC=abacavir; COBI=cobicistat; CNS=central nervous system; DTG=dolutegravir; EFV=efavirenz; eGFR=estimated glomerular filtration rate; ETR=etravirine; EVG=elvitegravir; FTC=emtricitabine; MI=myocardial infarction; PK=pharmacokinetics; PPI=protein pump inhibitor; RPV=rilpivirine; STR=single-tablet regimen; TDF=tenofovir.

Despite the availability of more than 25 antiretrovirals (ARVs), the number of recommended drug combinations remains limited for first-line ARV therapy and for switching to maintenance therapy. Patrick G. Yeni, MD, Bichat Medical School, Paris, France, said that there is a need for more drugs and strategies to accommodate very diverse individual constraints. Prof. Yeni would like to see an alternative to the conventional 3-drug combination regimen that replaces the 2 NRTI backbone, in particular in patients with boosted PI based-therapy. PI/r containing NRTI sparing regimens might include PI/r plus NNRTI, PI/r plus CCR5 inhibitor, PI/r plus INSTI, or PI/r mono (dual) therapy. The results of a recently completed meta-analysis suggests that virologically well-suppressed HIV-infected patients have a lower chance to maintain viral suppression when switching from combined ART to PI/r monotherapy [Mathis S et al. *PLoS One* 2011]. However, the consequences of failing this therapy may not be critical as there are some data indicating that the virus remains fully sensitive to PI and that the viral load returns to undetectable levels after the addition of the original baseline NRTIs.

Prof. Yeni discussed 3 ARV drugs that are currently in Phase 3 clinical development: EVG, dolutegravir (DTG), and COBI. Results from a study that compared the efficacy and safety of EVG with RAL in patients who failed previous ARV therapy showed similar efficacy and safety. The researchers concluded that since EVG can be given once daily versus twice daily for RAL, it might improve adherence [Molina JM et al. *Lancet Infect Dis* 2012].

In the SPRING-2 study [NCT01227824], a Phase 3 randomized, noninferiority study in treatment-naïve patients, once-daily DTG has been shown to be noninferior to twice-daily RAL when coadministered with 2 NRTIs over 48 weeks. The safety profiles were comparable. Adjusted treatment difference for DTG (88%) versus RAL (85%) was 2.5% (95% CI, –2.2 to 7.1). At virologic failure, no integrase nor NRTI mutations were detected in the DTG arm [Raffi F et al. IAC 2012 Abstract THLBB04]. In the Phase 3 SINGLE study [NCT01263015], the combination of DTG with ABC/3TC was shown to be superior to the fixed-dose combination TDF/FTC/EFV at 48 weeks, with less frequent discontinuation in the DTG arm [Walmsley S et al. ICAAC 2012 Abstract H-556b].

COBI has no ARV activity, but *in vitro* it is a potent and specific CYP3A inhibitor and inhibitor of MATE1 tubular transporter of creatinine. In a 48-week Phase 3 randomized study, FTC/TDF plus ATV/COBI was noninferior to FTC/TDF plus ATV/r in ART-naïve patients [Gallant JE et al. IAC 2012 Abstract TUAB0103]. The COBI arm had more Grade 3-4 hyperbilirubinemia (65% vs 57%; p=0.023) and more profound decreases in estimated glomerular filtration rate (–13 vs –9 mL/min; p=0.001) versus the ATV/r arm, but there was no PI resistance in the COBI group at 48 weeks.

Prof. Yeni concluded by noting that that several ARTs are in Phase 1 or 2 (Table 2), and "although the clinical application of individualized ARV therapy is improving, new drugs and strategies need to be tested."

Table 2. Some Antiretroviral Agents in Phase 1 or 2 Development.

Class	Agent	Phase
NRTIs	• BMS-986001 (Festinavir) • CMX-157 (prodrug of TFV) • GS-7340 (prodrug of TFV)	• Phase 2 • Phase 1 • Phase 2
NNRTIs	• Iersivirine (UK-453061) • MK-1439	• Phase 2 • Phase 2
PIs	• CTP-518 (deuterium modified ATV) • TMC-310911	• Phase 1 • Phase 2
INSTIs	• GSK-1265744	• Phase 1
CCR5 inhibitor	• Cenicriviroc (TBR-652)*	• Phase 2
Entry inhibitors	• BMS-663068 (prodrug of an attachment inhibitor) • Ibalizumab (aCD4 mab)	• Phase 2 • Phase 2

*Also inhibits CCR2; CCR=human chemokine receptor; INSTI=integrase inhibitor; NNRTIs=non-nucleoside reverse transcriptase inhibitor; NRTIs=nucleoside/nucleotide reverse transcriptase inhibitors; PIs=protease inhibitors.