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Nuke-Sparing Regimens for the Long-Term Care of HIV Infection

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Abstract

With the efficacy of antiretroviral therapy already guaranteed for all practical purposes, the main objective in the management of HIV-positive patients has moved to reduce and prevent potential long-term toxicities. Nucleos(t)ide-sparing regimens could enable the best to address this issue, with a wide range of current options that may allow adaptation to distinct patient populations. Monotherapy with boosted darunavir and lopinavir has been safely prescribed as maintenance therapy to stable patients on stable antiretroviral therapy, with prolonged viral suppression, nadir CD4 count > 200/mm^3 and without high-level baseline viremia or prior virologic failure. In the presence of these requirements, dual therapy with lamivudine plus boosted lopinavir or atazanavir has been shown to be equivalent to standard triple therapy. Other nucleoside-sparing dual therapies, especially using raltegravir combined with boosted darunavir or lopinavir and etravirine or rilpivirine in combination with boosted darunavir, have performed well as simplification strategies or rescue interventions in a wide spectrum of patients as long as drug resistance was absent. With current economical constrains, nuke-sparing regimens have attained a degree of maturity that makes it possible to anticipate that they will play an important role in the optimization of antiretroviral therapy in the near future. **(AIDS Rev. 2015;17:220-30)**

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Key words

Toxicity. Nucleoside analog reverse transcriptase inhibitor. Nucleoside-sparing regimen. Simplification strategy. Antiretroviral treatment. Monotherapy. Dual therapy.

Introduction

We are witnessing a paradigm shift in HIV treatment. The need for maintaining triple therapy (TT) permanently and in a static manner has been challenged from many quarters and at present poses a conceptual dilemma. There are, in essence, two factors that have pushed to review the TT paradigm. On the one hand, the toxicity of antiretroviral (ARV) drugs that, looking beyond efficacy, has become a major issue in antiretroviral therapy (ART), especially with regard to long-term outcomes. It is due to its often cumulative, subclinical features and the potential for interacting with comorbidities, aging and, in general, with any disease associated with the immune activation and inflammation that underlie HIV pathogenesis. This fact primarily affects nucleos(t)ide reverse transcriptase inhibitors (NRTI), which are used in combinations of two drugs in classic TT, enhancing their antiviral synergy, but at the cost of increasing their potential toxicity. In this way, NRTI-sparing regimens might constitute the first and most significant strategic attempt to reduce and prevent ART toxicity.

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The introduction of highly active ARV drugs with a very high resistance barrier has allowed to propose treatment simplification strategies that could reduce the number of drugs within ART regimens. We are basically referring to ritonavir-boosted protease inhibitors (PI/r) and perhaps dolutegravir (DTG). If expectations on efficacy are proven, NRTI-sparing regimens might provide a solution to the increasing concern on cumulative ARV toxicity. They might be a feasible and safe option against HIV in the near future.

There is a third aspect that may push these new strategies: their ability to reduce costs in a particularly large area of health expenditure, which poses obvious sustainability challenges for the developing world. Preliminary data suggest that the cost-efficiency of these treatments might be good, at least in certain populations.

The relevance of nucleoside analog toxicity

Several studies have shown the potential toxicity of NRTIs. The first agents within this class except lamivudine (3TC) and emtricitabine (FTC) (i.e., zidovudine, didanosine, zalcitabine and stavudine) are no longer prescribed, mainly because their potential for mitochondrial toxicity, often quick and intense, led to overt problems of intolerance (malaise, allergia, digestive, neurologic, metabolic and myeloid abnormalities, lipodystrophy, etc.). Older NRTIs soon lose their competitiveness against less toxic NRTIs, including lamivudine (and emtricitabine), abacavir (ABC) and tenofovir (TDF). However, whereas the low resistance barrier of either 3TC or FTC is a concern, toxicity issues remain a major drawback using either ABC or TDF.

After many years with a reputation for being drugs with very low toxicity profiles (except for the hypersensitivity syndrome associated with ABC), more rigorous and extensive analyses of their potential long-term adverse events have revealed significant issues. Besides being associated with an "excessive" incidence of idiosyncratic hypersensitivity symptoms (which has been much reduced with HLA-B57:01 genetic screening), ABC has been associated with increased cardiovascular morbidity and mortality[1]. Although it still remains controversial, results from several studies support a procoagulant effect of ABC[2].

Tenofovir has been specifically linked to kidney damage, which potentially can cause irreversible kidney failure[3]. Moreover, it has been associated to a higher incidence and prevalence of osteopenia[4,5]. Finally, it has been linked to a significant inhibition of telomerase activity, leading to telomere shortening and acceleration of the cellular aging process[6]. More recently it has been associated to persistent hypertransaminasemia in the absence of coinfection with hepatotropic viruses[7].

Because of the mitochondrial toxicity that characterizes NRTIs to different extents (which might be enhanced when used in combination), all NRTIs may cause adverse effects on the liver, bone marrow, artery walls, adipose tissue, gonads, muscle, nervous system, etc.[8]. This fact would make a nucleoside-sparing ARV regimen an attractive alternative option. Recent studies have shown that resolution of NRTI toxicity may follow their removal[9]. On the basis of commitment to patient's safety, simplified mono or dual therapies taking off NRTIs may be tried when TT is not strictly necessary.

The antiviral potency and resistance barrier of ritonavir-boosted protease inhibitors

The possibility of simplified ART approaches that would use fewer than three drugs required that one of the components should have strong antiviral effect along with high resistance barrier in order to compensate for the lack of drug(s). Until recently only ritonavir-boosted protease inhibitors (PI/r) provided this opportunity, i.e. lopinavir (LPV/r), atazanavir (ATV/r) and, especially, darunavir (DRV/r), all targeting the HIV protease with high affinity[10]. Previous studies have shown that PI/r-based regimens may work despite the accompanying drugs not displaying or in patients with poor drug adherence. The protective effect of these agents against drug resistance has resulted in a steadily fall of transmitted HIV drug resistance[11].

The cost-effectiveness of nucleoside-sparing regimens

The reduction in costs associated with the use of less than three-drug ARV regimens may be significant[12] and should not leave room for adopting an attitude of rejection[13].

Diverse nucleoside-sparing regimens

The need to prevent cumulative ARV toxicity and the clinical evidence of the robustness of new PI/r-based treatments has challenged the established paradigm of TT with two NRTIs plus a third distinct drug. With older drugs, however, outcomes were worse than with TT, mainly due to problems with tolerance and short-term

Table 1. Major antiretroviral monotherapy studies

Study	PI monotherapy vs. ART	No. of patients with PI vs. ART	Study design Follow-up	Prior VL	Prior ART	ITT (PI monotherapy vs. ART) VL < 50 copies/ml VL < 400 copies/ml	Mutations to PI
Arribas, et al. 2005 Pilot OK[15]	LPV/r vs. LPV/r + 2 NRTI	21 vs. 21	Randomized 48 weeks	< 50 copies/ml > 6 months	LPV/r + 2 NRTI	81 vs. 95.2% (< 50 copies/ml) 81 vs. 95.2% (< 400 copies/ml)	Monotherapy V77I; V77I + L63P; 1 patient without mutation to PI
Arribas, et al. 2009 OK04[16]	LPV/r vs. LPV/r + 2 NRTI	100 vs. 98	Randomized 96 weeks	< 50 copies/ml with cART	LPV/r + 2 NRTI	77 vs. 78% (< 50 copies/ml)	13% VF in MT vs. 22% in TT Low-level blips more frequent in the MT arm Reintroduction of nucleosides needed in 12% of MT
Meynard, et al. 2010 KALESOLO[17]	LPV/r vs. TT (cART)	87 vs. 99	Randomized, open 48 weeks, non inferiority	< 50 copies/ml > 6 months	TT (cART)	84 vs. 88% (< 50 copies/ml) 87 vs. 88% (< 400 copies/ml)	16% VF in MT vs. 12% cART (there were no key mutations to LPV/r in the MT arm)
Nunes, et al. 2009 KALMO[18]	LPV/r vs. 2 NRTI + PI or 2 NRTI + NNRTI	30 vs. 30	Randomized, open 96 weeks, non inferiority	< 50 copies/ml > 6 months	2 NRTI + PI or 2 NRTI + NNRTI	80 vs. 86% (< 80 copies/ml)	There was no virologic failure (VL < 500 copies/ml)
Arribas, et al. 2010 MONET[20]	DRV/r vs. DRV/r + 2 NRTI	127 vs. 129	Randomized 48 weeks	< 50 copies/ml 24 weeks	2 NRTI + NNRTI or 2 NRTI +PI	84.3 vs. 85.3% (< 50 copies/ml)	1 VF (> 50 copies/ml) in the monotherapy arm L33F 1 VF in the ART arm: M184V, V821T, L90M
Valantin, et al. 2012 MONOI ANRS 136[21]	DRV/r vs. DRV/r + 2 NRTI	106 vs. 105	Randomized, open, non inferiority 96 weeks	< 50 copies/ml 4 weeks	DRV/r + 2 NRTI	88% vs. 84% (< 50 copies/ml)	2 VF (> 50 copies/ml) DRV/r; 4 VF in triple arm No PI mutations detected in any arm
Antinori, et al. 2015 PROTEA[22]	DRV/r vs. DRV/r + 2 NRTI	137 vs. 136	Randomized. non inferiority 48 weeks	< 50 copies/ml in first line cART > 6 months	DRV/r + 2 NRTI	86 vs. 94% (< 50 copies/ml)	14% VF in MT vs. 6% (VL < 50 cop/ml in 48 weeks or withdrawal from study) 2 patients in MT arm with viremia in LCR, nadir CD4 < 200 cells/ul VF without genotypic resistance mutations.
Paton, et al. 2015 PIVOT[23]	MT vs. cART	296 vs. 291	Randomized, controlled, parallel, open, non inferiority (4 Nov 2008-28 July 2010)	< 50 copies/ml >24 weeks with no change in cART in the previous 12 weeks and CD4 > 100 cells/ul	cART	Primary objective loss of future ARV options: MT 2.1 vs. 0.7% in cART (no differences).	< 1% in MT arm with ATV developed mutation that conferred high resistance I50L

(Continue).

Table 1. Major antiretroviral monotherapy studies *(continued)*

Study	PI monotherapy vs. ART	No. of patients with PI vs. ART	Study design Follow-up	Prior VL	Prior ART	ITT (PI monotherapy vs. ART) VL < 50 copies/ml VL < 400 copies/ml	Mutations to PI
Karlström, et al. 2007[24]	ATV/r (300/100 mg)	30	Non-controlled, single arm, single center 72 weeks	< 20 copies/ml, for 12 weeks	cART	The study was terminated after 15 patients had been recruited because of 5 cases of VF that occurred between weeks 12 and 16	
Spagnuolo, et al. 2014 MODAT[25]	ATV/r vs. ATV/r + 2 NRTI	50 vs. 51	Randomized, multicenter, open, non-inferiority 96 weeks	< 50 copies/ml > 6 months	ATV/r + 2 NRTI	64 vs. 63%	28% VF in MT vs. 3.9% in TT VF: 2 consecutive VL > 50 copies/ml or discontinuation due to other causes. No drug resistance mutations in any arm
Pasquau, et al. 2014 Cohorte andaluza[27]	DRV/r	604	Non-controlled, single arm	< 50 copies/ml > 6 months	2 NRTI +PI (76%)	87% (< 50 copies/ml)	4.8% VF; no PI mutations

ART: antiretroviral therapy; VL: viral load; ITT: intent to treat; NRTI: nucleoside analogs, NNRTI: non-nucleoside analogs; VF: virologic failure; PI: protease inhibitor, MT: monotherapy, cART: combined antiretroviral treatment; TT: triple therapy; DRV/r: darunavir/ritonavir; LPV/r: lopinavir/ritonavir.

toxicity[14]. The first good initiative to assess whether monotherapy (MT) with a PI/r (specifically LPV/r) could perform comparable with TT was conducted in 2003[15].

The results were encouraging and set the stage for further therapeutic approaches towards ART simplification. Concerns on adverse events (i.e., gastrointestinal and metabolic) have reduced its application, despite being significantly cheaper. Taking advantage of the arrival of more potent and safer new ARVs, dual therapy (DT) with nucleoside-sparing agents has been tested. These studies have been done both for initial treatment as well as for treatment of patients on stable HIV-RNA suppression under TT. Overall, MT and DT trials have performed better in the simplification setting than with treatment of drug-naive patients. Therefore, this review will mainly focus on studies of MT and DT in patients on suppressed viremia on prior TT.

Antiretroviral monotherapies (Table 1)

Most monotherapy studies have compared their efficacy for maintaining viral suppression with TT regimens including two NRTIs in patients on stable ART and virologically suppressed. The first PI/r monotherapy study with LPV/r already mentioned above was the OK study[15], a pilot trial that showed that viral suppression with TT could be kept by shifting to LPV/r. Only 2/21 patients, who did not have good adherence to treatment, experienced loss of virological suppression. Interestingly, they did not select for PI resistance mutations.

Subsequently, these authors did more similar studies, such as OK04 (LPV/r twice daily [BID] vs. TT with LPV/r)[16] and MONET (DRV/r once daily [QD" versus any TT with a PI/r) that generally confirmed the non-inferiority of MT vs. TT[17]. Likewise, other groups tested MT with LPV/r[18-20], DRV/r[21,22], or both[23], usually with fairly encouraging results, in spite of some limitations that will be discussed later. In contrast, MT with ATV/r[24,25] did not perform as well, with treatment failure being more common as well as selection of PI resistance. Questions about insufficient central nervous system (CNS) penetration of ATV lessened the enthusiasm for MT using this agent.

Outside clinical trials, data from real-life patients on MT have been reported[26-31]. From more than 2,700 patients on MT, several conclusions can be drawn for patients on TT that switch to PI/r MT.

Within the clinical trial setting, > 1,500 patients have been examined and no stone has been left unturned in terms of comparative analysis. Furthermore, published cohorts of patients who have been exposed to MT in real

life add another > 2,700 patients[26-31]. So, data are sufficiently robust.

There are two meta-analyses[32,33] of clinical trials that attribute a lower overall ability to MT than TT for keeping viremia suppressed (–6% in both cases). However, differences in virologic response rates in all studies have been < 10%, except in one study[23], and the overall rate of patients receiving MT that continued with complete suppression was always > 80%.

The quality and intensity of viral suppression with MT was similar to TT when the preset target was plasma HIV RNA < 50 copies/ml), as shown in studies that have used ultrasensitive techniques[16,17].

In comparison with patients who received TT, patients on MT did not develop more resistance to ARVs[15-31,34] or experienced greater increases in proviral DNA[17,21], or benefit less from immune reconstitution[15-31], nor had more immune activation or proinflammatory markers[17,21,29,35-37]. It could be that inflammatory activity is only induced when viremia reaches a certain threshold, i.e., > 50 HIV RNA copies/ml[36,38], and that result in clinical consequences when it becomes elevated, i.e., > 10,000 copies/ml)[39], which did not occur in patients that failed on MT.

No significant abnormalities have been found in the "biological reservoirs", where ARV agents might not penetrate well. In several comparative analyses, neurocognitive impairment is not greater in patients on TT than MT[22,23,25,40,41], nor is there consistent indication of viral load (VL) escape in the cerebrospinal fluid[22,25,40,41], semen[42], or lymph tissues[43]. Nevertheless, there are lower concentrations of several ARV drugs in lymphoid tissues than in plasma or leukocytes[44]. This poses a problem even for TT, especially in anatomical sites such as the intestinal lymphatic system. However, anecdotal cases have reported neurological symptoms with loss of control of HIV replication in the brain of patients on MT.

Monotherapy should mainly be considered for patients who are well controlled, stable, with or without tolerance or toxicity problems while receiving TT. The discontinuation of NRTIs may provide benefits in terms of quality of life[20] and adverse events in the long term[23].

In the subgroup of patients receiving MT that fail to maintain VL< 50 copies/ml, it has been shown that:

- They generally recover the ability to keep viremia suppressed following resumption of prior treatment or other optimized ART regimen[15-31].
- If they continue receiving MT, two thirds may regain viral suppression[17,23,26,29].
- If viremia is maintained < 200/400 HIV RNA copies/ml, generally no PI resistance mutations are selected[15-31,34]. Thus, treatment failure on PI/r should not be considered until a level of 200 HIV-RNA copies/ml is reached.
- Proviral DNA and markers of immune activation and inflammation in MT patients only increase when loss of viral suppression is consistently elevated, but rarely when there is a blip or persistent low-level viremia[21,35,37-39].
- The inability to maintain virologic control on MT has been associated with poor adherence, nadir CD4 count < 200 cells/ml, high baseline VL, high proviral DNA, elevated immune activation, and short time with prior viral suppression on ART[17,21,22,30,31,45]. Taking all these limitations into consideration, the rate of success of MT could increase and even equal that of TT[22,31].
- Evidence for viral escape from reservoirs in patients on MT are scarce (CNS abnormalities, sexual transmission or enteropathy/malnutrition/bacterial translocation). Most reports have been limited to patients with nadir CD4 count < 200 cells/ml, high viral load, and prolonged viremia)[46].

With the advent of single-tablet boosted-PI regimens (darunavir with cobicistat, DRV/c), MT has become a truly attractive simplification option; a single tablet once a day.

Very recent and limited experiences of MT using dolutegravir (DTG) have been reported[47-49], with mean follow-ups of 24 weeks and apparently satisfactory results. However, in 4/82 patients with prior experience to integrase inhibitors, DTG resistance emerged, even with low-level viremia. At this time, the significance of this observation is uncertain and more studies are needed.

Dual antiretroviral therapies (Table 2)

As MT faces multiple challenges when compared to TT in non-inferiority studies, and new ARVs become available that are more potent and safer, novel treatment strategies continue to be explored. More recently marketed drugs include raltegravir (RAL), maraviroc (MVC), etravirine (ETV), rilpivirine (RPV) and dolutegravir (DTG). Upon their arrival, a new interest for nucleoside analog-sparing dual therapies has emerged. These regimens try to complement or reinforce PI/r. Whereas two early studies[50,51] showed that RAL in combination with LPV/r or DRV/r was non-inferior to TT, the results from larger trials have concluded differently for RAL in combination with either ATV/r or DRV/r[52-54]. The subanalysis of patients with baseline CD4 counts < 200 cells/ml and VL > 100,000 HIV RNA copies/ml[51] was particularly

worrisome for DT. Similar or even worst results were obtained when comparing the non-inferiority of DT with MVC + PI/r[55,56] and ETV + PI/r. Therefore at present, these DT modalities are currently discouraged for initial ART.

The case for DT as a simplification strategy for patients who are already receiving ART is quite different. In table 2 we have summarized the conditions, characteristics and results of the main DT studies conducted as treatment simplification for subjects experiencing virological failure. The following conclusions can be drawn from a careful analysis of all of them:

- Most of these studies suffer from methodological shortcomings, such as a small population size, lack of randomization, or heterogeneity of the population, although taken all together they include more than 1,250 patients.
- Even in simplification strategies for patients who have viral suppression, MVC + DRV/r and RAL + ATV/r combinations are inferior to TT in maintaining virologic control[57,58] and prevent emergence of resistance[59]. In contrast, RAL + LPV/r[60] and RPV + DRV/r[61] have shown comparable results to TT. No studies have been reported so far using RAL + DRV/r as a simplification strategy. However, the good results obtained in drug-naive patients[51] are encouraging.
- Dual therapy of RAL + LPV/r[62,63] or ETV + DRV/r[64-66] in patients experiencing virological failure have provided high efficacy in achieving and maintaining virologic control, opening new scenarios beyond simplification strategies for these DT regimens. They constitute the first proof-of-concept that nucleoside-sparing regimens can be used as rescue ART to prevent or avoid NRTI toxicity.
- Given that most nucleoside-sparing regimens include PI/r, emergence of drug resistance is anecdotal when they are used in patients with viral suppression. Data available regarding the impact on proviral DNA levels and markers of immune activation and inflammation are scarce, although RPV + DRV/r was claimed to produce better $CD8^+$ responses than TT[61].
- As nucleoside-sparing DT regimens include ARVs with improved safety profiles, they would result in better tolerance and facilitate adherence in the long-term[56,58,67,68].
- Cost savings will be significant as these regimens include less drugs.

Pursuing the prevention of ART toxicities in greater depth, DT without NRTI nor PI/r have been tested in several studies, which are recorded at the end of table 2, specifically ETV + RAL. However, although the majority of patients who receive this combination maintain viral suppression, the few subjects who experience virological failure select for resistance to RAL and/or ETV[69,70].

A latest DT that has moved forward is based on 3TC + PI/r. Despite not being a nucleoside-sparing regimen, it would avoid NRTI toxicity given the safety profile of 3TC. Moreover, since 3TC is already marketed as a generic product, low cost is an important advantage. Studies with 3TC + LPV/r[71,72] and 3TC + ATV/r[73,74] have already been published. Likewise, data on 3TC + DRV/r (DUAL study NCT02159599) will soon be available, and hopefully will confirm results from a retrospective cohort[75].

Altogether, results of DT studies allow drawing the following conclusions:

- The overall number of patients included is more than 1,100 patients[71-74]. The studies have a well-controlled design that compares DT to TT, with no significant methodological problems and are applied to a homogeneous patient population that has virologic control and is stable on their first line of ART and with no history of virological failure.
- The virological efficacy results of these DTs comply in every case with the criteria of non-inferiority with respect to TT[71-74], so they have already begun to appear in the recommendations with a high level of evidence in the antiretroviral treatment guidelines.
- Neither is there more emergence of resistance nor more blips nor greater incidence of low-grade viremia[71-74]. No data are available on the levels of proviral DNA or markers of immune activation and inflammation, but if these changes were dependent on the degree of viremia or antiretrovirals, then we could expect no adverse changes in these DTs.
- With respect to toxicity, these studies show that after switching to these DTs, a tendency towards improvement occurs in almost every testing parameter, including kidney function and bone mineral density[72-75].
- If the problem with “biological reservoirs” that can be had with MT is reproduced with DT is something that has been studied in depth in the SALT Study. And it has been shown that the cognitive impairment associated with HIV infection does not progress during exposure to DT, and that it is similar, no matter from what perspective it is viewed, to that presented by patients receiving TT[76].
- Since these are DTs that include 3TC, which is already available as a generic drug, it is obvious

Table 2. Major dual antiretroviral therapies

Study	TLA vs. ART	Number of TLA vs. ART	Design Follow up time	Prior VL	Prior ART	ITT (TLA vs. ART) VL < 50 copies/ml	Mutations to PI
Raffi, et al. 2014 NEAT	RAL (BID) + DRV/r (800/100) QD vs. DRV/r (800/ 100 mg) QD + TDF/FTC QD	401 vs. 404	Randomized 1:1 open 96 weeks	> 1,000 copies/ml	Naive	82.2 vs. 86.2%	17.8% VF in the RAL + DRV/r arm vs. 13.8% DRV/r + TDF/FTC (VF: reduction < 1 log in week 18; VL ≥ 400 copies/ml week 24; VL > 50 copies/ml week 32 and onwards) No mutations in the ART arm In the TLA arm 5 patients had integrase mutations (L65A, A155H)
Kozal, et al. 2012 SPARTAN	ATV/r + TDF/ FTC vs. ATV/r + RAL	31 vs. 63	Randomized 2:1 24 weeks	≥ 5,000 copies/ml	Naive	63.3 vs. 74.6%	1 (3.3%) VF in ATV/r + TDF/FTC vs. 6 (9.5%) (VF week 24 VL ≥ 400 copies/ml) 4 patients in the ATV/RAL arm developed RAL resistance
Taiwo, et al. 2011 ACTG A5262	DRV/R (800/100) QD + RAL (400) BID	112	Non-randomized, Single arm TLA 48 weeks	≥ 5,000 copies/ml	Naive	71%	28 (25%) VF (increase > 0.5 log/ml in week 4 or 12; or VL > 50 copies/ml in week 24; or VL > 50 copies/ml week 24) 5 patients had integrase mutations (Q148Q/R, 2 with N155H/N; Q148K/Q, N155H/N; N155H)
Mills, et al. 2013 A4001078	MVC 150 mg QD + ATV/r 300/100 mg vs. TDF/FTC 300/200 mg + ATV/r 300 mg/ 100 mg	60 vs. 61	Randomized 1.1 48 weeks	≥ 1,000 copies/ml	Naive	74.6 vs. 83.6%	25.4% VF in MVC arm vs. 16.4% TDF/FTC (VF VL > 50 copies/ml in week 48) 3 patients in each arm had VL > 500 copies/ml No selection of resistance nor tropism changes
Ofotokun, et al. 2012 KITE	LPV/r 400/ 100 mg + RAL 400 mg BID vs. LPV/r 400 mg 100 mg + NRTI	40 vs. 20	Randomized 2:1 48 weeks	< 50 copies/ml	Pretreated: LPV/r 400/100 mg + NRTI	92 vs. 88%	No resistance mutations in any arm
Amin, et al. 2015 SECOND-LINE[6]	LPV/r 400/ 100 mg + RAL 400 mg BID vs. LPV/r BID + 2-3 NRTI QD	270 vs. 271	Randomized 1:1, open. 96 weeks	£ or > 100,000 copies/ml	Pretreated: 2 NRTI + NNRTI	80.4 vs. 76.0% VL < 200 copies/ml	Resistance in the control arm vs. RAL: NRTI 12.5 vs. 3.1%; PI 3.1 vs. 1.5%; integrase 1.4 vs. 25.3% (VF HIV RNA > 200 copies/ml).
Ruane, et al. 2015 INROADS	ETV 400 mg + DRV/r 800/ 100 mg QD	54	Phase 2b, non-randomized, open, multicenter 48 weeks		Naive Pretreated	89%	7 VF (VL < 50 copies/ml at week 48)

(Continue).

Table 2. Major dual antiretroviral therapies *(continued)*

Study	TLA vs. ART	Number of TLA vs. ART	Design Follow up time	Prior VL	Prior ART	ITT (TLA vs. ART) VL < 50 copies/ml	Mutations to PI
Gazzola, et al. 2014	ETV + DRV/r	68	Non-randomized, retrospective, multicenter 24 months	VL detectable in 50% of patients	Pretreated with at least 5 prior regimens: 61.3% mutations to PI, 70% to NNRTI	88.8%	VF > 40 copies/ml at 6 months
Portilla, et al. 2014 BITER	ETV + DRV/r (600/100 mg BID or 800/ 100 mg QD)	99	Non-randomized, retrospective, multicenter 24 weeks	< 1,000 copies/ml 75.7% < 50 copies/ml	Pretreated with 33% NRTI + IP/r 17% NNRTI 23% IP/r + NNRTI 13% IP/r + INI 14% others	89%	1 VF without mutations (VF > 50 copies/ml week 24)
Cahn, et al. 2014 GARDEL	LPV/r + 3TC (150 mg) BID vs. LPV/r + 2 NRTI	217 vs. 209	Randomized 1:1 phase III, open 48 weeks	> 1,000 copies/ml	Naive	88.3 vs. 83.7%	10 (4.7%) LPV/r + 3TC vs. 12 (5.9%) LPV/r + 2 NRTI (VF: in week 24 > 400 copies/ml in 2 assays, or week 48 > 50 copies/ml in 2 assays). No mutations to PI in any arm. M184V in the ART arm.
Arribas, et al. 2015 OLE	LPV/r + 3TC vs. LPV/r + 2 NRTI	123 vs. 127	Randomized 1:1 48 weeks	< 50 copies/ml ≥ 6 months	Pretreated with: LPV/r + 2 NRTI	87.8 vs. 86.6%	3 VF per arm with no resistance mutations (VF: 2 VL > 50 copies/ml in a row)
Mondi, et al. 2015 ATLAS	ATV/r (300/ 100 mg) + 3TC (300 mg)	40	Simplification, prospective, single arm 144 weeks	< 50 copies/ml ≥ 3 months	Pretreated: 2 NRTI + ATV/r (300/100 mg)	77.5%	There were 2 VF with no resistance mutations (VF: > 2 consecutive VL > 50 or > 1,000 copies/ml)
Perez-Molina, et al. 2015 SALT	ATV/r (300/ 100 mg) + 3TC (300 mg) vs. ATV/r (300/ 100 mg) + 2 NRTI	143 vs. 143	Randomized 1:1 48 weeks	< 50 copies/ml ≥ 6 months	Pretreated with ATV/r (300/100 mg) + 2 NRTI	84 vs. 78%	6 (4%) ATV/r + 3TC vs. 10 (3%) ATV/r + 2 NRTI had VF (VL > 50 copies/ml in 2 assays ≥ 6 months). Only one M184V mutation in the ART arm
Reynes, et al. 2013 PROGRESS	LPV/r + RAL BID vs. LPV/r + TDF/ FTC QD	101 vs. 105	Randomized, open 96 weeks	VL 4.25 copies /ml (2-6)	Naive	66.3 vs. 68.6% (VL < 40 copies/ml)	Genotypic tests performed in 8 patients in the DT arm and INI mutations found in 3 (IN G140/S, Q148/H; N155H; N155H, G163/R); one also had mutations to PI: V32I, M46I, I47V. Genotypic tests performed in 5 patients in the ART arm and in only one was M184V detected

TLA: nucleoside-sparing therapy; ART: combined antiretroviral treatment or triple-therapy; ETV: etravirine; DRV/r: darunavir/ritonavir; NNRTI: non-nucleoside analog; INI: integrase inhibitor; RAL: raltegravir; TDF/FTC: tenofovir/emtricitabine (300/200 mg); MVC: maraviroc; LPV/r: lopinavir/ritonavir; PI: protease inhibitor; ATV/r: atazanavir/ritonavir; 3TC: lamivudine; DT: dual therapy; VL: viral load; VF: virologic failure; ITT: intent to treat; BID: twice daily; QD: once daily.

that this will entail a significant reduction in pharmaceutical costs. If we further consider that their efficacy is the same as that of TT at an early simplification stage, we must assume that they will become the dominant mode of action in cost/effectiveness terms.

In short, DTs using 3TC + PI/r in patients with stable viral suppression and no history of virological failure provide added efficacy to MT in exchange for an apparently very slight increase in potential toxicity and costs. We can still continue to improve these DTs with new PI/r in a single tablet regimen (DRV/c and atazanavir with cobicistat (ATV/c), which will mean a reduction of one tablet in regimens that until now have involved 3-4 pills daily.

The possibility of using ATV unboosted with ritonavir, by increasing the dose from 300 to 400 mg/day (ATV_{400}), also represents a new opportunity for simplification. The non-inferiority of ATV_{400} with respect to ATV/r has already been demonstrated in TT. And recently there have been reports published of small but encouraging experiences with a DT using 3TC + ATV_{400}[77-78], in which although there was no reduction in the number of tablets, there was a reduction in toxicity and the price of ritonavir.

Very recently, a novel DT approach that used 3TC and DTG both as initial ART[79] and as a simplification strategy in patients with virologic suppression was announced[49,80]. The results look very good, but these are studies conducted with very few patients and very limited follow up. One out of 51 cases described DTG resistance and it is obvious that more solid studies will be needed to draw conclusions.

Conclusions

The population infected with HIV exhibits an increased risk for morbidity and mortality from diseases that are not directly related with viral infection, but influenced by the potential toxicity of ART, especially of NRTIs. Therefore, strategies aiming to improve safety while maintaining viral suppression are eagerly pursued. In this context, regimens designed without NRTI combinations and that mainly involve boosted PIs (nucleoside-sparing regimens) have emerged as an attractive option with the advantage of reducing ART costs. Several nucleoside-sparing regimen options are available and each may better fit distinct patient profiles.

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