Moving Away from Ritonavir, Abacavir, Tenofovir, and Efavirenz (RATE) - Agents That Concern Prescribers and Patients: A Feasibility Study and Call for a Trial

Amit C. Achhra*, Mark A. Boyd, Matthew G. Law, Gail V. Matthews, Anthony D. Kelleher, David A. Cooper

The Kirby Institute, UNSW Australia, Sydney, New South Wales, Australia

Abstract

Objectives: Regimens sparing RATE (ritonavir, abacavir, tenofovir, efavirenz) agents might have better long-term safety. We conducted a feasibility exercise to assess the potential for a randomised trial evaluating RATE-sparing regimens.

Design: Observational.

Methods: We first calculated RATE-sparing options available to an average patient receiving RATE agents. We reviewed treatment history and all resistance assays from patients attending the St. Vincent's Hospital (Sydney) clinic and receiving ≥ 2 RATE agents (n = 120). A viable RATE-sparing regimen with 2 or 3 fully-active agents was constructed from the following six 'safer' agents: rilpivirine or etravirine; atazanavir; raltegravir; maraviroc; and lamivudine. Activity for each drug was predicted as 1 (full-activity), 0.5 or 0 (no activity) using the Stanford mutation database. The utility of maraviroc was calculated assuming both maraviroc activity and inactivity where unknown. The analysis was restricted to regimens for which supporting evidence was identified in the literature or conference proceedings. Finally, we calculated the proportion of patients in the nationally representative Australian HIV Observational Database (AHOD) cohort receiving ≥2 RATE agents (n = 1473) to measure the potential population-level uptake of RATE-sparing agents.

Results: Assuming full maraviroc activity, 117(97.5%) and 107(89.2%) individuals had at least one option with 2 or 3 active RATE-sparing agents, respectively. Assuming no maraviroc activity this decreased to 113(94.2%) and 104(86.7%), respectively. In AHOD, 837(56.8%) patients were receiving ≥2 RATE agents.

Conclusion: Feasible treatment switch options sparing RATE agents exist for the majority of patients. Understanding the pros and cons of switching stable patients onto new RATE-sparing regimens requires evidence derived from randomised controlled trials.

Introduction

While the development of antiretroviral therapy (ART) has seen tremendous success, there are ongoing concerns regarding the short- and long-term safety and tolerability of some of the common contemporary ART drugs. These agents and their associated concerns include: (i) Ritonavir (booster dose): long-term inhibition of CYP450, tolerance (diarrhoea) and dyslipidemia [1]; (ii) Abacavir: hypersensitivity [1], association with cardiovascular events,[1–3] and potency [4]; (iii) Tenofovir: long-term concern for bone and renal disease [5] and possibly heart failure [2]; and

(iv) Efavirenz: neuropsychiatric and cognitive effects [6] and dyslipidemia [7], (collectively termed RATE agents in this paper). These agents are often used in combination, thereby compounding their toxicity profile.

Newer, apparently safer, more tolerable drugs continue to be approved, but the data derived from their clinical development is generally limited to their use in first-line or late salvage ART. There is a need for evidence on how agents can be innovatively combined and sequenced in order to optimally replace RATE agents and in turn achieve better long-term outcomes. A few recent small studies of novel, unconventional regimens have been

reported and attest to the growing interest in more fully exploiting the opportunities offered by the growing HIV armamentarium. [8] Also, the SECOND-LINE [9], EARNEST [10] and the GARDEL [11] trials confirmed that 2 fully active agents are sufficient to achieve virological success, particularly in populations naïve to protease inhibitors (PIs).

Before planning a full scale trial evaluating RATE-sparing agents, we conducted a preliminary feasibility study to identify key metrics needed for planning such a trial. We had two key objectives: (i) in an average patient receiving ≥2 RATE agents, how many feasible RATE-sparing regimen options containing 2 or 3 fully-active agents are available if they were to switch?; and (ii) what proportion of HIV+ individuals at the population level receiving successful ART have ≥2 RATE agents as components of their regimen and might be expected to benefit from RATE-sparing options?

Methods

Study setting, population and analyses

Analysis of the St. Vincent's Hospital's database to calculate RATE-sparing options. For objective(i), we conducted a detailed review of the individual records of the patients attending the St. Vincents Hospital's ambulatory care clinic (the Hospital database). This database was chosen as it provided access to detailed treatment history, tropism test, all archived resistance mutations and clinical history available in each patient. The retrospective study on the St. Vincent's Hospital's database was approved by the St. Vincent's Hospital Human Research Ethics Committee, Sydney, Australia. Informed consent from participants was not obtained for this study. Requirement for informed consent for this study was waived by the above mentioned Ethics Committee. All of the data generated was made available in de-identified format to the study team.

We analysed the data from all patients enrolled in clinics under the following investigators: MAB, ADK, GM and DAC. Patients had to be receiving ≥2 RATE agents, in active follow-up (last visit within one year of March 2013), virologically suppressed (<200 copies/mL measured on at least 2 occasions more than 7 days apart) and not known to be hepatitis-B infected. We reviewed patient demographics, treatment history and resistance and tropism assay reports. Given that the resistance assay has been standard of care in Australia for some years, most patients were expected to have had one performed at the time of virological failure.

We defined a new regimen option as a RATE-sparing regimen constructed from a pool of the following six agents approved for use in Australia: rilpivirine or etravirine (cannot be used together); atazanavir (cannot be used with rilpivirine or etravirine because of possible unfavourable drug-drug interactions); raltegravir; maraviroc; and lamivudine. These agents were chosen for their proven efficacy and good safety profile. Also, from the PI class, only atazanavir is approved for use without a ritonavir booster. We limited consideration to raltegravir as the only integrase inhibitor available in Australia in the period we performed this analysis, but it could can be potentially be replaced by other integrase-inhibitors entering the market which will only increase the number of possible RATE sparing combinations available.

To predict drug activity we entered all recorded patient mutations (including archived results) in the Stanford mutation database version-6.3.0 (June 2013) [12]. The predicted activity was scored as 1 (susceptible or potential low-level resistance), 0.5 (low-level/intermediate resistance) and 0 (high-level resistance). Integrase inhibitor mutations were not available, but given that most

patients had only been exposed to raltegravir in their most recent regimen (with complete virological suppression), full activity was assumed. The HIV tropism test for predicting maraviroc activity had been performed at the discretion of the attending physician as the part of routine care using V3 Loop DNA assay. [13] A feasible regimen 'option' could either have a total score of 2 or 3 (i.e. containing 2 or 3 fully active agents respectively). Since the HIV tropism test was unavailable for the majority, options were calculated assuming both maraviroc activity = of 1(full activity) or 0 (where activity unknown).

Finally, since most of the RATE-sparing regimens were unconventional, we conducted a review of the peer-reviewed literature (using MEDLINE database) and major conference presentations to identify regimens for which there was at least some empirical support (defined as at least one study showing at least 24 or 48 week virological efficacy >80%). The search was conducted using key words for each of the agents in consideration (or their respective ART classes) using Boolean operators. We restricted the search to articles in English language published in the year 2006 or later. We included studies on regimens of interest regardless of study phase, number of patients or availability of a comparator arm.

Analysis of the AHOD cohort to quantify use of RATE agents in the population. For objective(ii), we analysed the data from the Australian HIV Observational Database (AHOD) cohort. The AHOD is an observational cohort study of HIV-positive individuals attending specialised general practitioner sites, sexual health clinics and tertiary referral centres throughout Australia. This study has been ongoing since 1999, and currently has 27 sites throughout Australia (including St. Vincent's Hospital Sydney). The AHOD study has been approved by the Human Research Ethics Committee of the University of New South Wales, Sydney, Australia, and all other relevant institutional review boards. Written informed consent was obtained from participating individuals in the AHOD study. The details of the AHOD study design have been published elsewhere [14].

We identified patients in the AHOD who were in active follow-up (documented visit within one year of March 2013 data transfer), receiving ART, virologically suppressed (HIV RNA < 200 copies/mL) at their last visit, and not known to be co-infected with hepatitis B (HBsAg negative). Our aim was to identify the proportion of such patients receiving ≥2 of RATE agents at their last follow-up visit and describe their demographic and treatment-history characteristics.

All analyses were performed using Ms Excel (Microsoft) and STATA ver. 12 (STATA Corp, Texas, USA).

Results

The St. Vincent's Hospital's database

A total of 120 patients from the Hospital database matched the selection criteria and were included in analyses. Table-1 describes their characteristics. They had been receiving ART for a median of 8 years (IQR: 4.4–12.9) and about 17% had exposure to integrase inhibitors. An HIV tropism test for predicting maraviroc activity was unavailable or unsuccessful in 54.2% and 7.5% of patients, respectively and 19 (15.9%) patients had full expected activity of the maraviroc. All HIV tropism tests were available within the last year (earliest one was in March-2012). About 16% of patients had no expected activity of either unboosted atazanavir or lamivudine.

Table-2 describes the number of available RATE-sparing regimen options under various scenarios. Assuming maraviroc activity = 1 where unknown, 117 (97.5%) and 107 (89.2%)

Table 1. Patient characteristics in the Hospital Database (n = 120).

Characteristics	N(%)
Gender- Male	113(94.2)
Age as at June 2013, mean(SD) years	43(9.4)
Race- Caucasian	114(95)
HCV positive	13(10.8)
Year of HIV diagnosis, Median (IQR)	2001(1991–2006)
Transmission mode	
MSM	83(69.2)
Other	13(10.8)
Unknown	24(20)
Cumulative duration of ART in years, median (IQR)	8.2(4.4–12.9)
History of mono/dual therapy exposure	19(15.9)
Class exposure ever	
PI	71 (59.2)
NNRTI	92 (98.9)
Integrase inhibitor	21(17.5)
CCR5 or other	6(5)
Class resistance ever*	
PI	20 (16.6)
NRTI	28 (23.3)
NNRTI	18(15)
All 3 classes	13(10.8)
Treatment experience**	
First line without substitutions	42(35.3)
First line with substitutions	43(36.1)
Second line or beyond	34(28.3)
Maraviroc activity based on tropism test	
Active	19(15.9)
Inactive	27(22.5)
Test unsuccessful***	9(7.5)
Unknown	65(54.2)
Five most common regimens	
TDF+FTC+EFV	44 (36.7)
TDF+FTC+ATV/r	22(18.3)
TDF+FTC+DRV/r	10(8.3)
ABC+3TC+EFV	9(7.5)
TDF+FTC+DRV+RTV+RAL	8(6.7)
Sub-optimal activity score to agents of interest***	
Rilpivirine	
-Score = 0.5	7(5.8)
-Score = 0	6(5)
Etravirine	
-Score = 0.5	11(9.1)
-Score = 0	2(1.7)
Atazanavir	
-Score = 0.5	1(1.8)
-Score = 0	20 (16.7)
3TC/FTC	
-Score = 0.5	4(3.3)

Table 1. Cont.

Characteristics	N(%)
-Score = 0	19(15.9)

individuals had at least one option with a score of 2 or 3, respectively. This decreased to 113 (94.2%) and 104 (86.7%), respectively, on assuming maraviroc inactivity where unknown.

The literature review indicated that direct or indirect support was available for many novel regimens, mainly in the form of small pilot studies [8] (key studies summarised in Table-S1 [15–30]. These included studies of the following two-drug regimens: raltegravir+maraviroc [16]; raltegravir+atazanavir [17–22] as well as with other protease inhibitors [31–33]; maraviroc+atazanavir [23,24], lamivudine +atazanavir (evidence available for only boosted atazanavir) [25,34], and raltegravir+etravirine [26,28,29]. It can be reasonably assumed that adding a third compatible agent to the above two-drug regimens would offer at least equal efficacy (e.g. adding maraviroc to raltegravir+etravirine [28–30]). The only exception might be in the case of raltegravir combined with other agents with a relatively low genetic barrier to resistance (e.g. raltegravir with rilpivirine and lamivudine; or raltegravir with rilpivirine and maraviroc) which were not included in the analyses.

Table-2 also describes a number of available RATE-sparing regimen options for which we could identify supporting evidence. Although the median number of available regimen options decreased in all of the scenarios, there was no appreciable change in the proportion of patients without any option remaining.

The AHOD cohort

Of the 1473 eligible patients in AHOD, 837 (56.8%, 95% confidence interval: 54.2%–59.4%) were receiving ≥2 RATE agents. Table-3 provides the characteristics of patients in AHOD who were receiving ≥2 RATE agents. Patients with ≥2 RATE agents had been receiving ART for a median of 10.7 (interquartile range (IQR): 4.1–15) years, 38% with a history of mono/dual therapy exposure in the past; they had been exposed to a median of 3 classes of drugs; 13.7% had been exposed to integrase inhibitors. The most common RATE agent used was tenofovir (76.9%) followed by ritonavir (in boosting dose) (55.7%).

Discussion

Our analysis of patients in one hospital-based clinic suggested that most patients receiving ≥2 RATE agents would be expected to have at least one viable RATE-sparing regimen switch option containing 2 or 3 fully-active agents This remained the case when we restricted our assessment to only those regimen options which have shown promise in publicly presented studies. In our analysis of the AHOD we found that up to 57% of HIV-positive individuals under treatment in Australia currently have ≥2 RATE agents in their regimen and might benefit from a RATE-sparing option. These findings suggest that there exits the potential to perform randomised trials to evaluate RATE-sparing regimens. Such trials would provide valuable guidance on how best to combine and sequence ART agents to maximise patient safety and preserve future treatment options.

Most of the regimens proposed and considered as 'viable' in this study have not been rigorously tested in clinical trials and might be regarded as unconventional, and perhaps as possessing a lower genetic barrier to the selection of resistance. However, there has

Table 2. Number of treatment options under various scenarios in the Hospital database.

Assumption for Maraviroc use	Options with score of 2			Options with score of 3		
	Median number of options (IQR)	Most common number of options (%)	Number of individuals with zero options (%)	Median number of options (IQR)	Most common number of options (%)	Number of individuals with zero options (%)
If R5 tropism assumed in those unavailable	12(7–12)	12(62.5)	3(2.5)	10(4–10)	10(62.5)	13(10.8)
If R5 tropism not assumed in those unavailable	7(7–7)	7(64.2)	7(5.8)	4(4–4)	4(64.2)	16(13.3)
Number of treatment options for which there was some support in the literature under various scenarios in the Hospital database						
If R5 tropism assumed in those unavailable	5(3–5)	5(61.7)	3(2.5)	7(3–7)	7(62.5)	13(10.8)
If R5 tropism not assumed in those unavailable	3(3–3)	3(65.0)	7(5.8)	3(3–3)	3(64.2)	16(13.3)

Table 3. Characteristics of those receiving ≥2 RATE agents and <2 RATE agents in AHOD.

Characteristics	Receiving ≥2 RATE agents (n = 837)	Receiving <2 RATE agents (including no RATE agents) (n = 636)
	N(%)	N(%)
Gender- Male	790(94.4)	598(94)
Age (mean± SD) years	50.1(±10.4)	52.3(±11.3)
HCV positive	87(11.5)	53(9.2)
Cumulative duration of cART in years (median IQR)	10.7(4.1–15)	13.1(5.4–15.1)
History of mono/dual therapy exposure	399(47.7)	346(54.4)
History of mono/dual therapy exposure for at least 30 days	318 (38.0)	236(37.1)
Class exposure ever		
PI	570(68.1)	374(58.8)
NNRTI	722(86.3)	546(85.9)
Integrase inhibitor	116(13.7)	201(31.6)
CCR5	10(1.2)	12(1.9)
Total number of classes exposed to		
Median	3	3
Mean	2.7	2.8
Exposure to >2 classes	466 (55.7)	371(58.3)
RATE agents		
Ritonavir	466(55.7)	102(16.0)
Abacavir	246(29.4)	203(31.2)
Tenofovir	644(76.9)	265(41.7)
Efavirenz	386(46.1)	10(1.6)
None	0(0)	56(8.8)

Note: RATE = ritonavir, abacavir, tenofovir and efavirenz. cART = combination antiretroviral therapy with at least 3 drugs.
doi:10.1371/journal.pone.0099530.t003

been growing interest in testing novel combinations of ART agents, which exclude nucleoside(tide) and older non-nucleoside reverse transcriptase inhibitors (N(t)RTIs and NNRTIs, respectively) as well as ritonavir (booster dose) [35]. The SECONDLINE [9] and EARNEST [10] trials suggest that a strategy of carefully selecting 2 fully-active agents is likely to be successful. Other studies suggest that raltegravir combined with one or two other active agents (e.g. a protease inhibitor or maraviroc or a second generation NNRTI) is a viable option in patients, even those with extensive treatment experience. [28,30,36] In the NEAT001 trial in ART-naïve individuals, the combination of raltegravir+ boosted-darunavir performed well although less well in those with baseline VL>100,000 copies/mL. [37] In the 48-week LATTE phase-2b trial, the combination of a doultegravir-analogue with rilpivirine performed equally well in comparison to conventional EFV-containing triple therapy in maintaining virological suppression after induction with conventional NtRTI-containing triple therapy. [15] One small study (Roc N Ral) study [38], the virological failure rate in the raltegravir+maraviroc arm was high (21%). Of note, the tropism was analysed using Geno2Pheno (rather than phenotypic assay) and failure was linked to adherence <80%.

A few limited studies on unboosted atazanavir and raltegravir show encouraging results in terms of virological success and safety profile, although hyperbilirubinemia might be an issue with unboosted atazanavir containing regimens, especially if atazanavir is used at a dose of 300 mg twice-daily. [18] However, after>10 years in clinical use atazanavir is not known to be associated with adverse long-term outcomes, atazanavir at 200 mg twice daily provides adequate pharmacokinetic coverage and discontinuation for hyperbilirubinaemia is relatively uncommon. [39] Similarly, combining boosted-atazanavir with maraviroc has shown promising results (comparable virological response at 48 weeks to tenofovir + emtricitabine + boosted-atazanavir regimen) [24]. Further, replacing boosted atazanavir with un-boosted atazanavir (as considered in this study) in virologically suppressed individuals appears to be safe and effective. [40].

In one small single-arm trial, ART-naïve patients achieving virological suppression with a four drug combination of tenofovir, emtricitabine, maraviroc and raltegravir, safely stopped the N(t)RTI component after 24 weeks without any failure 24 weeks after stopping the N(t)RTIs. [16] In another study of patients who had experienced triple-class failure, a regimen of 3 fully-active agents (raltegravir, maraviroc and etravirine) demonstrated 96% virological efficacy and improvement in lipid profiles at 96 weeks of follow-up [29]. Finally, a dual drug combination of raltegravir and etravirine in treatment experienced patients without past NNRTI failure has shown promising results. [26] Of note,

- HIV+
- on RATE-containing ART
- VL<50 copies/ml for at least 6 months
- <=2 past failures
- Tropism test, if unknown

Panel of physician reviews treatment history and archived mutations if any. They then construct a regimen from the pool of RATE-sparing agents

No RATE-sparing regimen option?

Exclude

Randomisation stratified by availability of 2 or 3 fully active RATE-sparing drugs

Continue current regimen

RATE-sparing regimen

- Primary endpoint: plasma Viral load <200 copies/mL
- Secondary endpoints:
  o Discontinuation of the regimen for toxicity.
  o Viral load <50 copies/mL.
  o Extensive safety monitoring including bone, renal, cardiovascular and body-composition parameters as well as markers of inflammation.
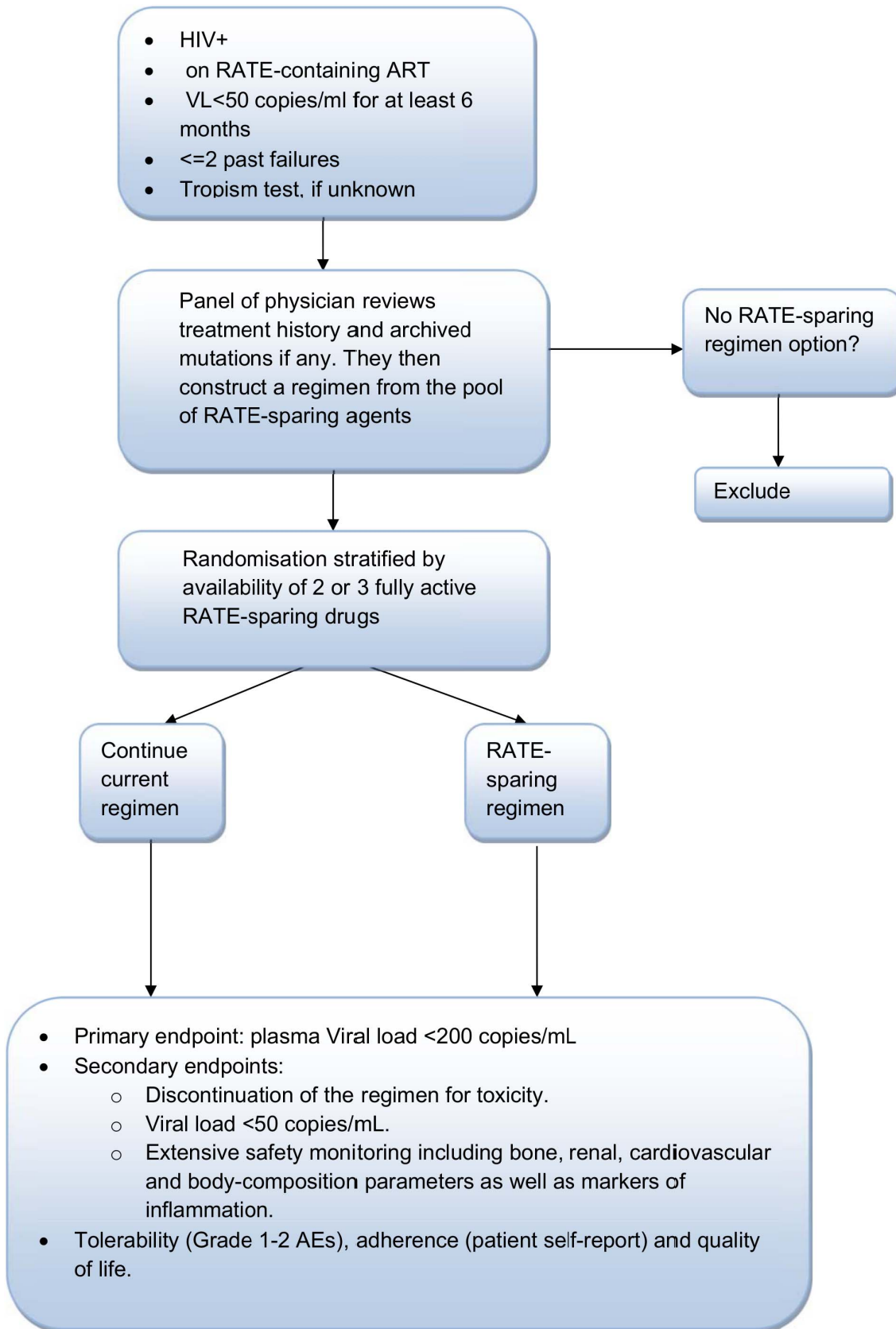- Tolerability (Grade 1-2 AEs), adherence (patient self-report) and quality of life.

Figure 1. Proposed trial for evaluating RATE-sparing options.
doi:10.1371/journal.pone.0099530.g001

emergence of integrase mutations in dual therapy regimens containing raltegravir tend to occur in those with HIV RNA> 100,000 copies/mL at the time of switch. [28,41] Overall, these studies support the notion that 2 or 3 fully-active pharmacologically compatible agents result in robust virological response in carefully selected patients.

Despite these observations there is a clear need for trials to rigorously evaluate RATE-sparing regimens, not only to demonstrate their virological success but also their expected greater tolerability and safety. Given the concern for possible resistance emergence in those with high viral loads, trials could initially focus on virologically suppressed patients with no or limited history of treatment failure and high expected adherence. The scheme of a proposed trial design is represented in Figure 1. The end-points include virological suppression as well as extensive safety monitoring. Ideally such a trial should have hard clinical end-points to demonstrate safety. At the very least it would need to be a 96 week study monitoring metabolic, renal, bone and body composition parameters. Drop-out or premature switching in the control arm would be handled by intention-to-treat follow-up and analysis to minimise bias.

The following additional/alternative trial strategies would be worth considering: (i) enrolling patients thought to be at a high risk of a chronic disease such as cardiovascular disease and therefore most likely to benefit from the trial. [42] This may be relevant for some drugs, for example abacavir. However, drugs such as ritonavir are undesirable even to low-risk patients; (ii) providing physicians with a menu of 3–4 reasonable RATE-sparing regimens so that the trial has enough power to make some conclusions about individual regimens as well as about the overall strategy of switching. Given that a vast majority of our patients had >0 activity for most of the RATE-sparing agents (except about 16% fully resistant to atazanavir and lamivudine eachTable-1), it is clear that a list of 3–4 RATE-sparing regimen options would be available to most patients.

Our study has limitations. Firstly, it was a retrospective survey of patient data. It analysed data from patients attending a single large tertiary hospital centre in Sydney (for objective i). It is possible that more complicated or difficult to manage patients may have been selectively referred to this centre, resulting in lesser generalizability of our findings. However, this may have only resulted in underestimation of the actual number of options available to patients in general. Also, patient characteristics in the Hospital database were broadly similar to those in AHOD, suggesting minimal selection bias. Second, the Hospital database may not have accurately captured comorbidities and concomitant

medication data which may impact the number of suitable options available to a patient. However, the agents considered for treatment options are known to have only few serious drug-drug interactions or contraindications. Our assessment of the recorded data on comorbidities and concomitant medications did not affect our conclusions. We therefore do not believe this limitation would seriously undermine the number of options available. We did not consider use of atazanavir and etravirine together as an option (due to drug-drug interactions), though a recent study suggests that the use of a higher dose of atazanavir in such a combination may not be necessary. [43] Allowing these two agents in combination would increase the number of options available. Finally, many NRTI-sparing regimens may require twice daily dosing frequency and ≥1–2 pills/day. This may impact the adherence. However, both maraviroc (with a boosted atazanavir) and etravirine have pharmacokinetic and clinical data supporting once-daily dosing [24,44], and raltegravir is being studied in a 1200-mg once-daily formulation. Some RATE-sparing regimens might well become available with fewer pill burden/infrequent dosing.

In summary, our study suggests that most patients using RATE agents have viable RATE-sparing switch options which include 2 or 3 fully active agents in the switch regimen. The use of RATE drugs is common and a significant proportion of HIV-positive individuals might be expected to benefit from such options. There is a need for fully powered randomised trials to rigorously evaluate this strategy in order to optimise long-term patient outcomes.

Supporting Information

Table S1 Summary of regimens supported by the literature.
(DOCX)

Acknowledgments

Author Contributions

Conceived and designed the experiments: MAB MGL DAC ACA. Performed the experiments: ACA. Analyzed the data: ACA MAB. Contributed reagents/materials/analysis tools: ADK GVM MAB DAC. Wrote the paper: ACA. Contributed to the interpretation and review of the manuscript: MAB MGL DAC ADK GVM.

References

1. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, et al. (2012) Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA 308: 387–402.
2. Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, et al. (2011) Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS 25: 1289–1298.
3. Costagliola D, Lang S, Mary-Krause M, Boccara F (2010) Abacavir and cardiovascular risk: reviewing the evidence. Curr HIV/AIDS Rep 7: 127–133.
4. Hill A, Sawyer W (2009) Effects of nucleoside reverse transcriptase inhibitor backbone on the efficacy of first-line boosted highly active antiretroviral therapy based on protease inhibitors: meta-regression analysis of 12 clinical trials in 5168 patients. HIV Med 10: 527–535.
5. Calza L (2012) Renal toxicity associated with antiretroviral therapy. HIV Clin Trials 13: 189–211.
6. Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, et al. (2011) Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology 76: 1403–1409.
7. van Leth F, Phanuphak P, Stroes E, Gazzard B, Cahn P, et al. (2004) Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. PLoS Med 1: e19.

8. Achhra AC, Boyd MA (2013) Antiretroviral regimens sparing agents from the nucleoside(tide) reverse transcriptase inhibitor class: a review of the recent literature. AIDS Res Ther 10: 33.
9. SECOND-LINE Study Group, Boyd MA, Kumarasamy N, Moore CL, Nwizu C, et al. (2013) Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. Lancet 381: 2091–2099.
10. Paton N, Kityo C, Hoppe A, Hakim J, van Oosterhout J, et al. (2013) A pragmatic randomised controlled strategy trial of three second-line treatment options for use in public health rollout programme settings: the Europe-Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Kuala Lumpur, Malaysia.
11. Cahn P, The GARDEL Study Group. (2013) Dual therapy with Lopinavir/Ritonavir (LPV/r) and Lamivudine (3TC) is non-inferior to standard triple drug therapy in Naïve HIV-1 infected subjects: 48-week results of the GARDEL Study. 14th European AIDS Conference Brussels, Belgium.

12. Stanford University. HIV Drug Resistance Database. HIV Drug Resistance Database. Available: http://hivdb.stanford.edu/. Accessed 25 June 2013.

13. Tu E, Swenson LC, Land S, Pett S, Emery S, et al. (2013) Results of external quality assessment for proviral DNA testing of HIV tropism in the Maraviroc Switch collaborative study. J Clin Microbiol 51: 2063–2071.

14. Australian HIV Observational Database (2002) Rates of combination antiretroviral treatment change in Australia, 1997–2000. HIV Med 3: 28–36.

15. Margolis D, Brinson C, Eron J, Richmond G, LeBlanc R, et al. (2014) 744 and Rilpivirine as Two-Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results [Abstract 91LB]. 21st Conference on Retroviruses and Opportunistic Infections. Boston, USA.

16. Cotte L, Durant J, Brochier C, et al (2013) Safety and efficacy of a Maraviroc-Raltegravir combination following a 6 month induction phase with Maraviroc-Raltegravir-Tenofovir-Emtricitabine in naïve HIV-1 infected patients with CCR5 Virus: interim analysis of the No Nuc No Boost study [Abstract WEPE511]. IAS 2013. Kaula Lumpur, Malaysia.

17. Ward DJ, O'Neil DJ (2013) Nucleoside-sparing antiretroviral regimens in clinical practice. [Abstract H-659]. 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver USA.

18. Kozal MJ, Lupo S, DeJesus E, Molina JM, McDonald C, et al. (2012) A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naive HIV-infected patients: SPARTAN study results. HIV Clinical Trials 13: 119–130.

19. Carey D, Pett SL, Bloch M, Wand H, MacRae K, et al. (2012) A randomized study of pharmacokinetics, efficacy, and safety of 2 raltegravir plus atazanavir strategies in ART-treated adults. J Acquir Immune Defic Syndr 60: 143–149.

20. Cordery DV, Hesse K, Amin J, Cooper DA (2010) Raltegravir and unboosted atazanavir dual therapy in virologically suppressed antiretroviral treatment-experienced HIV patients. Antivir Ther 15: 1035–1038.

21. Allavena C, Mounoury O, Rodallec A, Reliquet V, Billaud E, et al. (2009) Efficacy and safety of an NRTI-sparing dual regimen of raltegravir and ritonavir-boosted protease inhibitor in a triple antiretroviral class-experienced population. HIV Clin Trials 10: 337–340.

22. Gupta S, Lataillade M, Farber S, Kozal MJ (2009) Raltegravir with unboosted atazanavir 300 mg twice daily in antiretroviral treatment-experienced participants. J Int Assoc Physicians AIDS Care 8: 87–92.

23. Wilkin TJ, McKinnon JE, DiRienzo AG, Mollan K, Fletcher CV, et al. (2009) Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy: final 48-week clinical and virologic outcomes. J Infect Dis 199: 866–871.

24. Mills A, Mildvan D, Podzamczer D, Fatkenheuer G, Leal M, et al. (2013) Maraviroc once-daily nucleoside analog-sparing regimen in treatment-naive patients: randomized, open-label pilot study. J Acquir Immune Defic Syndr 62: 164–170.

25. Di Giambenedetto S, Fabbiani M, Colafigli M, Ciccarelli N, Farina S, et al. (2013) Safety and feasibility of treatment simplification to atazanavir/ritonavir + lamivudine in HIV-infected patients on stable treatment with two nucleos(t)ide reverse transcriptase inhibitors + atazanavir/ritonavir with virological suppression (Atazanavir and Lamivudine for treatment Simplification, AtLaS pilot study). J Antimicrob Chemother 68: 1364–1372.

26. Calin R, Valantin M, Simon A, Paris L, Tubiana R, et al. (2013) Raltegravir/etravirine dual therapy as a virologically safe treatment option in suppressed HIV-1-infected patients without previous NNRTI failure. 7th International AIDS Society Conference on HIV Pathogenesis Treatment and Prevention. Kuala Lumpur, Malaysia.

27. Monteiro P, Perez I, Laguno M, Martinez-Rebollar M, Gonzalez-Cordon A, et al. (2014) Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study. J Antimicrob Chemother 69: 742–8.

28. Imaz A, Llibre JM, Mora M, Mateo G, Camacho A, et al. (2011) Efficacy and safety of nucleoside reverse transcriptase inhibitor-sparing salvage therapy for multidrug-resistant HIV-1 infection based on new-class and new-generation antiretrovirals. [Erratum appears in J Antimicrob Chemother. 2011 Sep; 66(9): 2194]. J Antimicrob Chemother 66: 358–362.

29. Nozza S, Galli L, Bigoloni A, Nicola G, Pogliaghi M, et al. (2011) Durability and safety of a novel salvage therapy in R5-tropic HIV-infected patients: maraviroc, raltegravir, etravirine. J Acquir Immune Defic Syndr 56: e113–115.

30. Tashima K SL, Andrade A, et al (2013) Omitting NRTI from ARV regimens is not inferior to adding NRTI in treatment-experienced HIV+ subjects failing a protease inhibitor regimen: the ACTG OPTIONS study [Abstract 153LB]. 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, Georgia, USA.

31. Bedimo R, Drechsler H, Turner D, Moore T, Ghormley J, et al. (2011) RADAR study: Raltegravir combined with boosted Darunavir has similar safety and antiviral efficacy as tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naive patients. Rome.

32. Ofotokun I, Sheth AN, Sanford SE, Easley KA, Shenvi N, et al. (2012) A switch in therapy to a reverse transcriptase inhibitor sparing combination of lopinavir/ritonavir and raltegravir in virologically suppressed HIV-infected patients: a pilot randomized trial to assess efficacy and safety profile: the KITE study. AIDS Res Hum Retroviruses 28: 1196–1206.

33. Jansen A, Colbers EPH, van der Ven A, Richter C, Rockstroh JK, et al. (2013) Pharmacokinetics of the combination raltegravir/atazanavir in HIV-1-infected patients. HIV Medicine 14: 449–452.

34. Casado JL, de la Calle C, del Palacio M, Perez-Elias MJ, Moreno A, et al. (2013) Short communication: lamivudine plus a boosted-protease inhibitor as simplification strategy in HIV-infected patients: proof of concept. AIDS Res Hum Retroviruses 29: 588–591.

35. Taiwo B, Murphy RL, Katlama C (2010) Novel antiretroviral combinations in treatment-experienced patients with HIV infection: rationale and results. Drugs 70: 1629–1642.

36. Imaz A, del Saz SV, Ribas MA, Curran A, Caballero E, et al. (2009) Raltegravir, etravirine, and ritonavir-boosted darunavir: a safe and successful rescue regimen for multidrug-resistant HIV-1 infection. [Erratum appears in J Acquir Immune Defic Syndr. 2011 Nov 1;58(3): e102]. J Acquir Immune Defic Syndr 52: 382–386.

37. Raffi F, Babiker A, Richert L, Molina J, George E, et al. (2014) First-Line Raltegravir (RAL) + Darunavir/Ritonavir (DRV/r) is Non-inferior to Tenofovir/Emtricitabine (TDF/FTC) + DRV/r: The NEAT 001/ANRS 143 Randomised Trial [Abstract 84LB]. 21st Conference on Retroviruses and Opportunistic Infections. Boston, USA.

38. Katlama C, Assoumou L, Valantin MA, Soulie C, Duvivier C, et al. (2014) Maraviroc plus raltegravir failed to maintain virological suppression in HIV-infected patients with lipohypertrophy: results from the ROCnRAL ANRS 157 study. J Antimicrob Chemother.

39. Achenbach CJ, Darin KM, Murphy RL, Katlama C (2011) Atazanavir/ritonavir-based combination antiretroviral therapy for treatment of HIV-1 infection in adults. Future Virol 6: 157–177.

40. Squires KE, Young B, DeJesus E, Bellos N, Murphy D, et al. (2012) ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. HIV Clin Trials 13: 233–244.

41. Taiwo B, Zheng L, Gallien S, Matining RM, Kuritzkes DR, et al. (2011) Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). AIDS 25: 2113–2122.

42. Carr A, Hoy J, Pozniak A (2012) The ethics of switch/simplify in antiretroviral trials: non-inferior or just inferior? PLoS Med 9: e1001240.

43. Orrell C, Felizarta F, Nell A, Kakuda T, Lavreys L, et al (2013): Etravirine 200 mg twice daily combined with atazanavir/ritonavir 300/100 mg or 400/100 mg once daily in treatment-experienced patients: primary 48-week efficacy and safety analysis of the TEACH trial IAS. Kaula Lumpur, Malaysia.

44. Gazzard B, Duvivier C, Zagler C, Castagna A, Hill A, et al. (2011) Phase 2 double-blind, randomized trial of etravirine versus efavirenz in treatment-naive patients: 48-week results. AIDS 25: 2249–2258.