The relation between baseline HIV drug resistance and response to antiretroviral therapy: re-analysis of retrospective and prospective studies using a standardized data analysis plan

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To assess the relation between resistance to antiretroviral drugs for treatment of HIV-1 infection and virological response to therapy, results from 12 different studies were re-analysed according to a standard data analysis plan. These studies included nine clinical trials and three observational cohorts. The primary end-point in our analyses was virological failure by week 24. Baseline factors that were investigated as predictors of virological failure were plasma HIV-1 RNA, the number and type of new antiretroviral drugs in the regimen, and viral susceptibility to the drugs in the regimen, determined by genotyping or phenotyping methods. These analyses confirmed the importance of both genotypic and phenotypic drug resistance as predictors of virological failure, whether these factors were analysed separately or adjusted for other baseline confounding factors. In most of the re-analysed studies, the odds of virological failure were reduced by about twofold for each additional drug in the regimen to which the patient's virus was sensitive by genotyping methods, and by about two- to threefold for each additional drug that was sensitive by phenotyping.

Introduction

The frequent development of antiretroviral drug resistance complicates the management of patients with HIV-1 infection. Because resistance to a given antiretroviral can produce cross-resistance to other drugs of the same class, choosing the best 'salvage' therapy for patients who have failed one or more treatment regimens is a formidable challenge. Assays that assess HIV-1 drug susceptibility, either by genotyping or

phenotyping methods, may aid in the selection of appropriate salvage regimens, but their value in predicting response to antiretroviral therapies is still being established. Many retrospective and prospective studies of HIV drug susceptibility testing have been reported [1–15], but interpretation of results and assessment of their consistency is complicated by variability in such factors as study design, definitions of drug resistance, virological end-points, and methods of analysis. Differences in the way analyses control for potentially confounding covariates in different studies especially limits ability to interpret results across studies.

This article reports on standardized analyses of HIV-1 drug resistance conducted by the Resistance Collaborative Group (RCG), which was convened to assess the performance and utility of HIV-1 drug resistance assays in antiretroviral drug development and patient management. The RCG was composed of virologists, statisticians, and clinicians from academic institutions and pharmaceutical companies in the USA and Europe. A major goal of the RCG was to evaluate the existing clinical data for the extent to which HIV drug susceptibility assays predicted virological response to treatment among patients who have failed one or more combination antiretroviral regimens. The RCG investigators identified all clinical studies that had collected information on baseline drug resistance and virological response to antiretroviral treatment and that had been completed prior to April 21, 1999 [1–10,12–15]. These included both observational studies and randomized clinical trials conducted in North America and Europe. Studies with sufficient sample size to perform multivariate analyses were then re-analysed by the individual study investigators using a standardized data analysis plan developed by the RCG.

Methods

A data analysis plan (DAP) was distributed to all investigators that participated in the re-analysis of studies. The DAP specified the precise methods used to associate baseline measures of resistance and other known predictors of treatment response with virological response to antiretroviral therapy. The primary end-point for analysis was virological failure by week 24 (defined below); logistic regression was used to relate this end-point to a common set of covariates. Virological failure was defined as plasma HIV-1 RNA above the threshold of 400 copies/ml while on the original study regimen at study week 24 (or in a window between weeks 16 and 32). Other thresholds for failure could be used if they were specified in the original study protocol. Transient increases in HIV-1 RNA were not counted as virological failures, in other words patients whose HIV-1 RNA was greater than the threshold at week 24 but whose next measurement was below threshold despite no change in therapy. To evaluate the effect of early withdrawal from study medication, two analyses were required: a 'dropout as censored' (DAC) analysis, in which subjects who dropped out of the study without evidence of virological failure were treated as censored and excluded from analysis; and a 'dropout as failure' (DAF) analysis, in which such patients were counted as virological failures. For the DAC analysis, patients whose last value was above threshold were counted as virological failures only if any of the three following conditions applied: (i) the patient had at least two on-treatment HIV-1 RNA measurements ≥the baseline HIV-1 RNA value (confirmed non-responder); (ii) the reduction in HIV-1 RNA from baseline was <0.5 $\log_{10}$ HIV-1 RNA copies/ml for all values measured between and including weeks 4 through week 8 (lack of response); and (iii) the nadir of HIV-1 RNA was below 400 copies/ml (rebound). Patients who had no HIV-1 RNA measurements in the week 24 window (weeks 16–32) were excluded from all analyses.

Genotype analyses

For each drug, the RCG constructed a list of mutations for which there is evidence of a negative impact on the virological response to that drug (Table 1). The list was developed by the RCG to facilitate re-analyses of studies before these had been undertaken; it is not intended for use in clinical management of patients. Two measures of genotypic information were explored. The first, a genotypic sensitivity score, was based on the number of drugs in the study regimen to which the patient's virus was likely to be sensitive. In general, for each drug in the regimen a value of 0 was assigned if there was genotypic evidence of resistance to that drug in the patient's baseline virus, and a value of 1 if there was no genotypic evidence of resistance to that drug. There were, however, a few exceptions in which scores of 1.5 (M184V for adefovir) or 0.75 (zidovudine resistance mutations for stavudine, didanosine and zalcitabine) were assigned. The overall genotypic sensitivity score (GSS) was defined as the sum of the genotypic sensitivities for all the drugs in a patient's treatment regimen. The second measure consisted of one or more of the following variables: the number of PI mutations, the number of NRTI mutations and the number of NNRTI mutations from the list of mutations in Table 1. Mixtures of mutant and wild-type at the same codon were scored as mutant. Because the number of mutations present for a drug class not used in the study regimen was unlikely to be predictive of virological failure, only the classes of drugs in the study

Table 1. List of mutations associated with resistance to specific antiretroviral drugs used in the data analysis plan

Nucleoside reverse transcriptase inhibitors	
Zidovudine (ZDV)	K70R; T215Y or F; M41L; D67N; L210W; K219Q
Stavudine (d4T)	See MNR-1 and MNR-2, below (Note: V75T may be selected *in vitro* by d4T, but it is rare *in vivo* and not clearly associated with d4T failure. Therefore, it was not counted in a genotypic sensitivity score as indicative of d4T resistance.)
Didanosine (ddI)	L74V; K65R; M184V or I
Zalcitabine (ddC)	K65R; T69D; L74V; M184V or I
Lamivudine (3TC)	M184V or I
Abacavir (ABC)	Any three or more of the following: M184V; K65R; L74V; Y115F; T215Y or F; M41L; D67N; K70R; L210W; K219Q
Multi-nucleoside resistance-1 (MNR-1)*	Q151M; Secondary: A62V; V75I; F77L; F116Y (Note: higher levels of resistance may be seen when the secondary mutations listed above are present with G151M, but these mutations should not be counted in a genotypic sensitivity score unless Q151M is present.)
Multi-nucleoside resistance-2 (MNR-2)*	Three amino acids encoded by an insertion between RT codons 69 (69Ins) and 70; Secondary: A62V; M41L; D67N; K70R; L210W; T215Y or F; K219Q (Note: higher levels of resistance may be seen when the secondary mutations listed above are added to the 69Ins mutation, although those secondary mutations may not cause multinucleoside resistance by themselves and therefore should were not counted in a genotypic sensitivity score as indicative of multinucleoside resistance unless 69Ins was also present.)
Nucleotide reverse transcriptase inhibitor	
Adefovir (ADV)	K65R; K70E (Note: M184V causes increased susceptibility to ADV.)
Multi-nucleoside resistance-2 (MNR-2)‡	See nucleoside reverse transcriptase inhibitor section above for details
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine (NVP)	K103N; V106A; V108I; Y181C or I; Y188C or L or H; G190A or S
Delavirdine (DLV)	K103N; Y181C; P236L
Efavirenz (EFV)	K103N; Y188L; G190S or E; Secondary: L100I; K101E or Q; V108I; Y188H; P225H (Note: in some cases, higher levels of resistance may be seen when the secondary mutations listed above are added to the K103N mutation, although those secondary mutations may not cause resistance by themselves and therefore were not counted in a genotypic sensitivity score as indicative of resistance unless K103N was also present.)
Protease inhibitors	
Indinavir (IDV)	V32I; V82A or T or F; I84V; L90M
Ritonavir (RTV)	V32I; V82A or T or F or S; I84V; L90M
Saquinavir (SQV)	G48V; V82A or T; I84V; L90M
Nelfinavir (NFV)	D30N; V82F; I84V; L90M
Amprenavir (APV)	V32I; I50V; I84V

*This MNR profile is associated with resistance to ZDV, d4T, 3TC, ddI, ddC, and abacavir.
‡This MNR profile is associated with resistance to ZDV, d4T, 3TC, ddI, ddC, abacavir, and adefovir.
Further criteria were used for determining genotypic sensitivity scores:
(1) Adefovir-susceptible wild-type virus counts as 1.0 and adefovir hyper-susceptible RT M184V counts as 1.5.
(2) Primary analysis should not allow RT M184V reversal of ZDV resistance to be considered. In other words, ZDV resistance would be the interpretation whether or not RT M184V is also present. A second analysis using an interpretation of ZDV resistance reversal by M184V could have been done at the investigators option.
(3) In the absence of any of the mutations listed for d4T, ddI, or ddC in the table above, a genotypic sensitivity score of 0.75 was assigned for d4T, ddI, or ddC if three or more of the following mutations are present: RT M41L; D67N; K70R; L210W; T215Y or F; K219Q. This is based on data suggesting that there may be a cross-class effect of these mutations on responses to other NRTIs and that they may sometimes be selected *in vivo* by d4T, even though phenotypic cross-resistance has not been clearly defined *in vitro*.

regimen were modelled; hence, this measure comprised at most three variables.

Phenotype analyses

Phenotypic measures of resistance were based on the fold-resistance of the patient's isolate compared with a wild-type laboratory control and were handled as an ordered categorical variable. Two different cut-offs were used for categorizing patient's baseline virus as sensitive or resistant, one was based on the minimum cut-off for the assay (fourfold), and the other was based on a 10-fold cut-off indicative of high-level resistance. As with genotype, two measures of phenotypic information were explored. The first, a phenotypic sensitivity score, was based on the number of drugs in the study regimen to which the patient's virus was sensitive. For each drug in the regimen, a value of 0 was assigned if the patient's virus was resistant to that drug and 1 if the virus had greater than a four- or 10-fold decrease in susceptibility. The overall phenotypic sensitivity score (PSS) was defined as the sum of the phenotypic sensitivity values for all the drugs in the patient's regimen. The second measure consists of one or more of the following variables: the number of protease inhibitors (PIs), the number of nucleoside reverse transcriptase inhibitors (NRTIs) and the number of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the study regimen to which the patient virus had phenotypic sensitivity. Only the classes of drugs in the patient's regimen were modelled, because the number of drugs in a class not included in the study regimen is unlikely to be predictive of viro-

Table 2. Characteristics of the re-analysed studies

Name	**ABC Pooled**	**ACTG 333**	**ACTG 364**	**ACTG 372**	**CNAA 2007**
Investigators	Lanier *et al.* [8]	Para *et al.* [13]	Katzenstein *et al.* [7]	Hammer *et al.* [5]	Ait-Khaled *et al.* [1]
n with GT/PT	134/84	46/0	144/0	96/80	94/64
Treatment experience	Patients receiving at least 8 weeks of NRTI therapy prior to addition of ABC	Patients with at least 48 weeks of exposure to SQV and naive to all other PIs	Patients with prolonged NRTI exposure but naive to NNRTIs/PIs	Patients failing ZDV+3TC+IDV in ACTG 320. Group B: NNRTI naive. Group D: NNRTI-experienced	Patients failing combination therapy with at least one of the following PIs: IDV, RTV, SQV, or NFV
Treatment regimens	ABC+ZDV or ABC+ZDV+ddI, d4T or 3TC	Background NRTIs+SQVhgc, SQVsgc or IDV	2 NRTIs+NFV, EFV or NFV+EFV	Group B: EFV+ADV +ABC versus 1–2NRTIs+NFV versus placebo. Group D: ADV+ ABC+EFV+NFV	ABC+EFV+APV
Resistance test	GT (PE*); PT (Virco)	GT (PE)	GT (Stanford)	GT (Virco); PT (Virco)	GT (PE); PT (Virco)
Median baseline HIV-1 RNA (range) [IQR] (copies/ml)	3.7 (2.6–5.8)	4.1	4.1 [3.6–4.6]	4.6	5.1 (3.4–6.6)
Median baseline CD4 (range) [IQR] (cells/mm^3)	417 (11–1266)	240	323 [242–460]	196	160 [10–782]
Name	**GS 408**	**Stanford cohort**	**BC centre cohort**	**Frankfurt cohort**	**Swiss cohort**
Investigator	Miller *et al.* [9]	Zolopa *et al.* [15]	Harrigan *et al.* [6]	Miller *et al.* [12]	Lorenzi *et al.* [10]
N with GT/PT	161/0	54/0	58/53	0/50	62/0
Patient population	Patients with HIV-1 RNA >2500 and CD4 >200	PI failures	Patients beginning RTV/SQV	Patients starting six or more ARTs simultaneously with at least 24 weeks of follow-up	HAART failures (HIV-1 RNA >1000) despite good adherence
Treatment regimens	ADV+ background ART	2 NRTIs+ RTV/SQV	RTV/SQV alone or with NRTIs	'Mega' HAART	NFV plus other ARTs
Resistance test	GT (Pharmacia)	GT (PEB)	GT (Virco); PT (Virco)	PT (Virco)	GT (PEB)
Median baseline HIV-1 RNA (range) [IQR] (copies/ml)	Mean 4.1	5.0	4.8 [2.7–5.8]	5.5	5.2 [3.1–6.4]
Median baseline CD4 (range) [IQR] (cells/mm^3)	Mean 338	245	160 (10–560)	95	113 (4–633)

GT, genotyping; PT, phenotyping; ABC, abacavir; ZDV, zidovudine; IDV, indinavir; RTV, ritonavir; SQV, saquinavir; NFV, nelfinavir; ddI, didanosine; d4T, stavudine; 3TC, lamivudine; EFV, efavirenz; ADV, adefovir.
As described above, ACTG 372 appears twice in this table, one time as group B only (NNRTI-naive) and the other time including group D (patients with prior NNRTI exposure). ACTG 364 also appears twice, once including information from all three treatment arms of the study, and the second time including only the two, triple drug treatment arm and excluding the quadruple drug arm.
*PE, Perkin Elmer Applied Biosystems DNA Sequencer

logical failure.

Two types of analyses of virological failure were carried out. In the first, only the resistance variables were included in a model; in the second, analyses were adjusted for baseline confounding factors. These factors included: baseline $\log_{10}$ HIV-1 RNA, the presence or absence of a potent PI or NNRTI in the regimen (the patient must have been naive to PIs and/or NNRTI for the drugs to be considered potent), and the number of new drugs in the regimen. The latter two are referred to collectively as new drug covariates.

Studies re-analysed

The lead investigators of 14 studies were invited to participate in a workshop convened on April 21–22, 1999, by the Clinical Validation Subcommittee of the Resistance Collaborative Group. These studies included all of the ones that collected either genotype or phenotype data and that permitted exploration of the relationship between genotype and/or phenotype and virological failure. The Subcommittee concluded that despite the demonstration by the investigators of associations between genotype/phenotype and virological outcome, variability in the methods of analysis complicated interpretation of results. To provide an overview of results from all available studies, the Subcommittee developed a standardized DAP. Investigators were then invited to participate in a re-analysis of their studies using the DAP. The criteria for inclusion of a study in the re-analysis included having at least 24 weeks of follow-up and adequate sample size (approximately 50 or greater) for multivariate modelling. Of the 12 studies that met these criteria, six were clinical trials that compared different specified

therapies [1,5,7–9,13], two were clinical trials that compared the response to treatment selected on the basis of genotype versus standard of care [2,4], and four were observational cohort studies [6,10,12,15].

Results

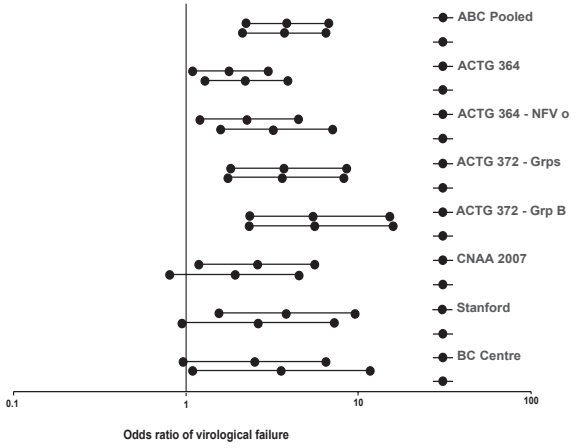
Table 2 summarizes the basic characteristics of the 10 retrospective studies included in our analyses. Analysis of the two prospective, genotype-based studies, GART and VIRADAPT, were carried out separately (see below). Eight of the retrospective studies provided information about baseline genotype and five had information about baseline phenotype. Of note, two analyses of ACTG 372 were performed, one restricted to subjects in group B and the other that included subjects from both groups B and D. Group B patients had prior exposure to zidovudine, lamivudine and indinavir but not to the NNRTI drug class, whereas Group D patients had prior exposure to NNRTIs. Two analyses were also performed for ACTG 364, one that included only the two, triple drug therapy arms in the trial (two NRTIs plus efavirenz or two NRTIs plus nelfinavir) and the other, which included the four drug arm (two NRTIs plus nelfinavir plus efavirenz). In addition, for two studies [9,10] the change in plasma HIV-1 RNA from baseline, rather than the virological failure end-point, was analysed and thus these two studies are not included in the composite analyses described below.

Figure 1 displays the odds ratios and 95% confidence intervals for virological failure associated with each 1.0 $\log_{10}$ higher baseline plasma HIV-1 RNA for the eight retrospective studies in which baseline genotype was available. The analysis that included only baseline plasma HIV-1 RNA as a covariate is shown as the top line in each pair of lines, and the analysis that adjusted for genotypic sensitivity score and other baseline confounders (new drug covariates) is shown as the bottom line in the pair. This figure shows the consistently important role of baseline plasma HIV-1 RNA in predicting virological failure, whether analyses are unadjusted or adjusted for new drug covariates or genotypic sensitivity score. In general, a 1.0 $\log_{10}$ higher baseline plasma HIV-1 RNA is associated with a two- to fivefold increase in the odds of virological failure.

Figure 2 shows the odds ratios and 95% confidence intervals for virological failure associated with each unit increase in baseline genotypic sensitivity score (GSS). The unadjusted odds ratios are shown as the top line of each pair and the ratios adjusted for baseline plasma HIV-1 RNA and new drug covariates as the bottom line in the pair. This figure shows a consistent trend that a higher GSS (in other words more drugs in the regimen without evidence of resistance) is associated with lower odds of virological failure, with the two exceptions being ACTG 372 group B and the adjusted analysis of ACTG 364 that included only triple drug treatment arms (four drug arm excluded). Note that the trend for ACTG 372 changes when the NNRTI-experienced group D patients are included, probably because inclusion of Group D increases the range of genotypic sensitivity scores. The small sample size of these studies results in wide confidence intervals for the odds ratios, making interpretation of the statistical significance of each individual study difficult; but the overall results supports the role of GSS as an important predictor of failure. The effect of each unit increase in GSS ranges between a slight increase to a 2.5-fold reduction in the odds of virological failure, with four of the six studies showing at least a twofold reduction in odds.

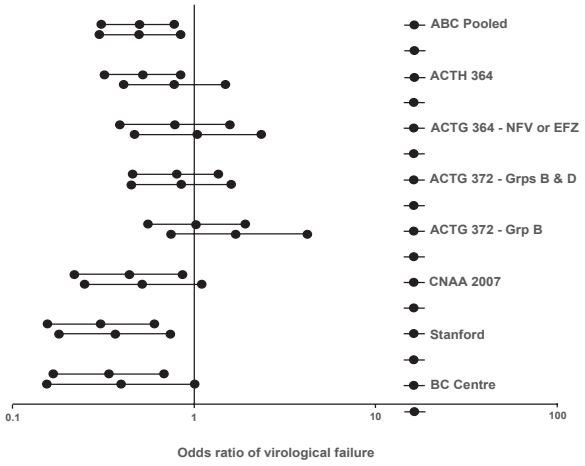
Figure 3 shows the effect of the number of NRTI mutations at baseline on the odds ratio for virological failure, adjusted only for the number of mutations to other classes of drugs (top lines) or for baseline HIV-1 RNA and new drugs covariates as well (bottom line). Similarly, Figure 4 shows the effect of the number of PI mutations at baseline on the odds ratios for virological failure. The figures show the odds ratios associated with each additional mutation and their 95% confidence bounds. The results show a consistent trend toward increasing odds of virological failure associated with each additional mutation in RT or protease. The observed range of effect varies from no effect to about a twofold increase in the odds of virological failure for

Figure 1. Baseline HIV-1 RNA (odds ratio per 1.0 $\log_{10}$ increase) unadjusted and adjusted for genotypic sensitivity score and new drug covariates.



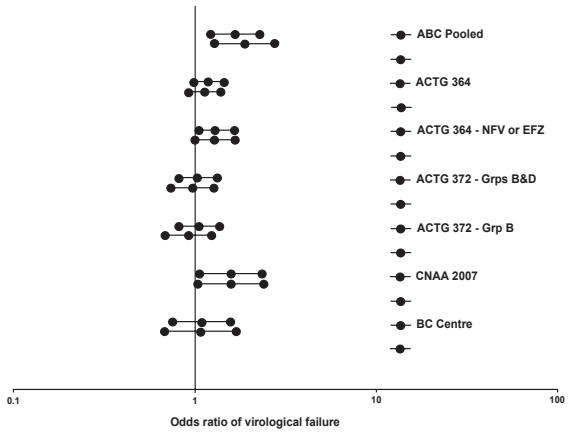
Top line in pairs: unadjusted for genotypic sensitivity score and new drug covariates. Bottom line in pairs: adjusted for genotypic sensitivity score and new drug covariates. Horizontal lines are 95% confidence intervals around the odds ratio point estimate.

Figure 2. Baseline genotypic sensitivity score (odds ratio per 1.0 unit increase)



Top line in pairs: unadjusted for baseline RNA and new drug covariates. Bottom line in pairs: adjusted for baseline RNA and new drug covariates. Horizontal lines are 95% confidence intervals around the odds ratio point estimate.

Figure 3. Baseline number of NRTI mutations (odds ratio per 1 additional mutation)



Top line in pairs: adjusted for mutations in drug classes other than NRTIs. Bottom line in pairs: adjusted for baseline HIV RNA and new drug covariates. Horizontal lines are 95% confidence intervals around the odds ratio point estimate.

each mutation. The effect appears more consistent for the number of PI mutations for the five studies in which these data were available.

Figures 5 and 6 shows the effect of baseline phenotypic sensitivity score (PSS), using four- and 10-fold cut-off points for resistance, respectively, on the odds of virological failure for the five studies in which this information was available (top line, unadjusted odds ratios; bottom line, adjusted odds ratio). The results show a consistent association between higher PSS and lower odds of virological failure. The strongest result is for the PSS based on the fourfold cut-off point. In general, for each unit increase in the PSS, odds of virological failure are reduced between two- and threefold.

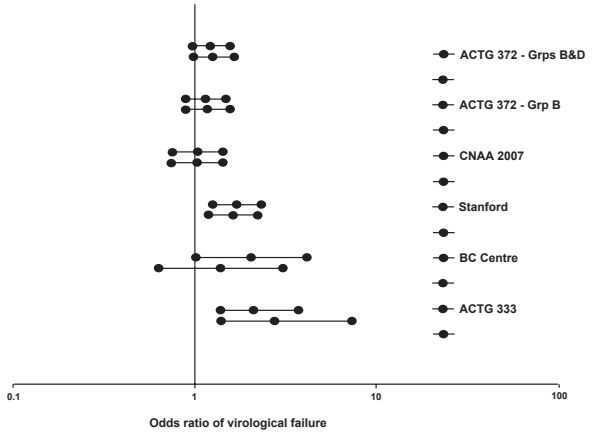
Figure 7 shows the effect of baseline GSS on the odds of virological failure in the prospective GART and VIRADAPT trials. These results are qualitatively similar to those of the retrospective studies, with only the 'no genotyping' (standard of care) arm in VIRADAPT failing to show an association between baseline GSS and the odds of failure.

In all the analyses described above, premature dropouts were treated as virological failures. The results of analyses in which dropouts were censored yielded similar results (data not shown).

Discussion

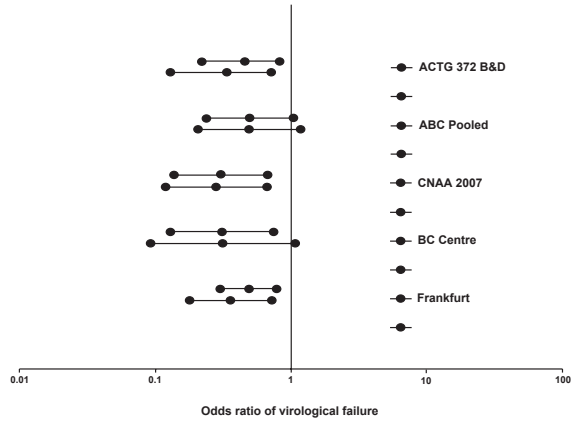
The goal of this study was to assess the consistency of the association between baseline resistance test results and response to antiretroviral therapy. To accomplish this, a diverse group of retrospective and prospective studies that had been presented at scientific meetings were re-analysed by the investigators using a standardized re-analysis plan developed by the RCG that controlled for important confounding variables. The analyses clearly show that resistance test results are associated with 24-week virological response to antiretroviral treatment across a broad range of treatment regimens and study population studies. This association is evident for both phenotypic and genotypic assays, and whether genotype was analysed by determining the number of NRTI- or PI-resistance mutations or by calculating the genotypic sensitivity

Figure 4. Baseline number of PI mutations (odds ratio per 1 additional mutation)



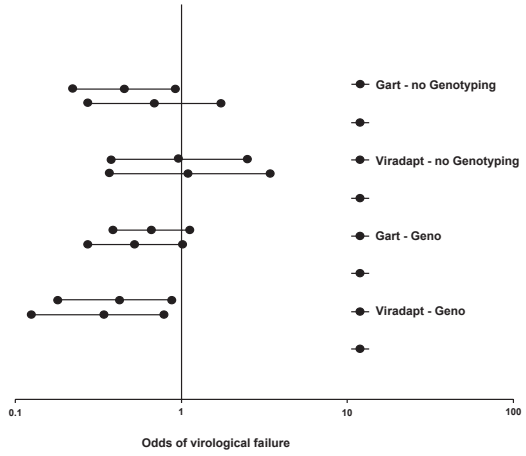
Top line in pairs: unadjusted for baseline RNA, new drug covariates and mutations in non-PI drug classes. Bottom line in pairs: adjusted for baseline RNA, new drug covariates and mutations in non-PI drug classes. Horizontal lines are 95% confidence intervals around the odds ratio point estimate.

Figure 5. Phenotype sensitivity score (odds ratio per 1.0 unit increase). Sensitivity was defined as ≥fourfold increase in IC_{50} compared to wild-type control.



Top line in pairs: unadjusted for baseline HIV-1 RNA and new drug covariates. Bottom line in pairs: adjusted for baseline HIV-1 RNA and new drug covariates. Horizontal lines are 95% confidence intervals around the odds ratio point estimate.

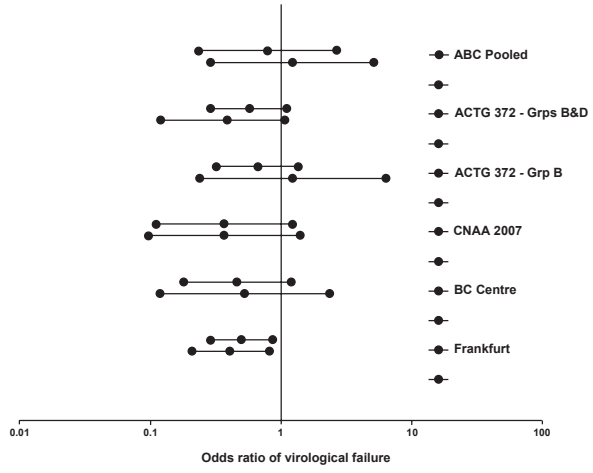
Figure 7. Prospective studies: baseline genotypic sensitivity score (odds ratio per 1.0 unit increase).



Top line in pairs: unadjusted for baseline HIV-1 RNA and new drug covariates. Bottom line in pairs: adjusted for baseline HIV-1 RNA and new drug covariates. Horizontal lines are 95% confidence intervals around the odds ratio point estimate.

score (GSS). The consistency of associations between genotyping results and virological outcome are noteworthy in that non-standardized genotyping methods were used by the different investigators. Standardized interpretation of the genotypes using the mutations in Table 1 may have been partly responsible for the consistency of the associations. Nevertheless, variability in the associations was noted; reasons for this variability may include varied genotyping methods [16,17], incomplete knowledge of mutations that confer resistance, and relatively small sample sizes. A single method was used for the phenotyping results [18], which may explain the greater consistency in the association with virological response among the five studies in which phenotype data was available.

Figure 6. Phenotypic sensitivity score (odds ratio per 1.0 unit increase). Sensitivity was defined as ≤10-fold increase in IC_{50} compared with wild-type control.



Top line in pairs: unadjusted for baseline HIV-1 RNA and new drug covariates. Bottom line in pairs: adjusted for baseline HIV-1 RNA and new drug covariates. Horizontal lines are 95% confidence intervals around the odds ratio point estimate.

These analyses, however, do not define the optimal way to use resistance test results for clinical management of patients. Only longer-term studies that investigate the role of specific mutations, individually and in groups, can determine their optimal clinical use. Nevertheless, cumulative sensitivity scores, such as the GSS and PSS, are likely to be useful approaches because they can summarize complex information into a simple score. Further research will also be required to better define what mutations or level of phenotypic resistance should be used in calculation of the cumulative scores and what sensitivity values should be assigned for each drug. The table of mutation used in the calculation of the GSS (Table 1) reflects a consensus reached by leaders in the field of which mutations would be useful in our re-analyses. The table is not intended for use in clinical management of patients. Important knowledge about the roles of specific mutations, individually and in combination, in treatment response is still accumulating. Further investigation of results from individual studies will help in updating these tables. In addition, the use of standard analytical methods applied to a broad range of studies, such as the one described in this report, can help define the best clinical use of drug resistance assays.

The results of these re-analyses add to the body of evidence supporting the importance of resistance

testing in antiretroviral drug development and virological response to therapy. Results of three prospective, randomized trials of regimen selection with the aid of individual patient genotype or phenotype compared to the current standard of care (no resistance results) support the clinical utility of resistance in patient management [2,4,19]. Several other ongoing prospective, randomized studies of resistance testing versus standard of care should provide additional insight into the utility of resistance information in a variety of clinical settings. Other important variables that are known or likely to affect virological response to therapy, such as baseline viral load and CD4 count, drug pharmacokinetics, and medication adherence should be incorporated in analyses of resistance information to maximize the predictive value of resistance testing and ultimately to improve patient outcome [20].

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