SUPPLEMENT: More efficacious drugs lead to harder selective sweeps in the evolution of drug resistance in HIV-1

Alison F Feder[1], Soo-Yon Rhee[2], Robert W. Shafer[2], Dmitri A Petrov[1,*], Pleuni S Pennings[1,3,*]

[1]Department of Biology, Stanford University, Stanford, CA

[2] Department of Medicine, Stanford University, Stanford, CA

[3] Department of Biology, San Francisco State University, San Francisco, CA

[*]Equal contribution

Running Head: Efficacious drugs lead to harder sweeps in HIV-1

Keywords:

Corresponding author:

Alison F. Feder

Department of Biology

Stanford University

Stanford

CA 94305

USA

Phone: 773 998 1409

Email: afeder@stanford.edu

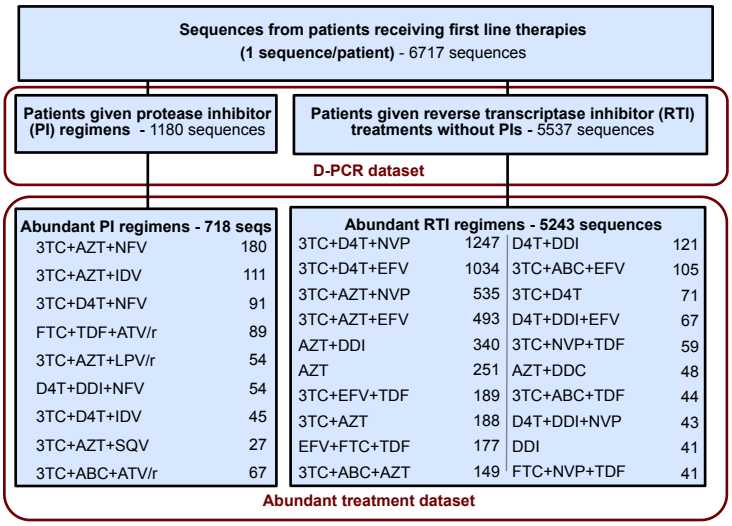

Figure 1: Summary of data subgroups and filtering Summary of all sequences from patients receiving first line therapy used throughout the analysis. The dataset is broken down into patients receiving protease inhibitor (PI) therapy with reverse transcriptase inhibitors (RTIs) and patients receiving only RTIs. The abundant treatment dataset shows treatments given to many patients within our dataset. For full filtering parameters for the abundant dataset, see *materials and methods*. Counts of sequences for each treatment are given.

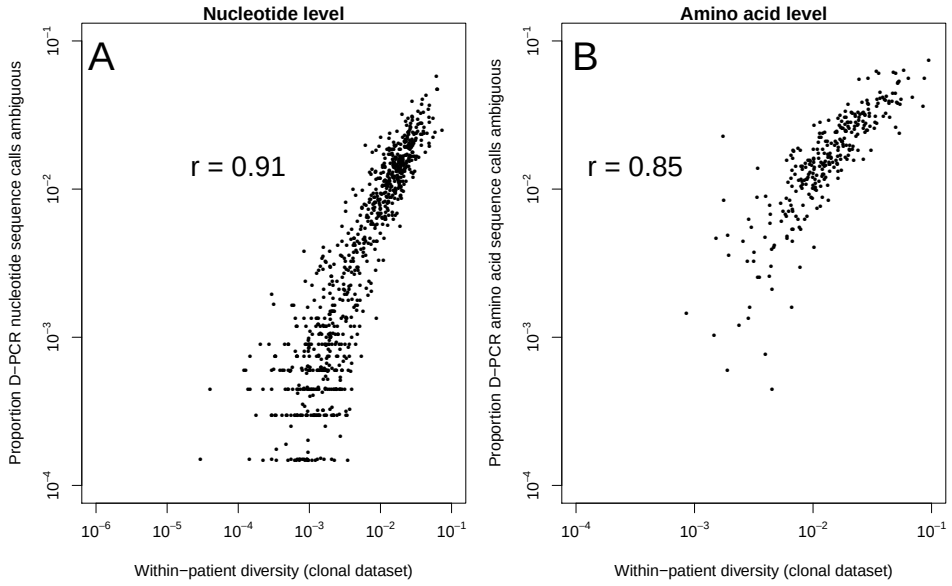

Figure 2: Correlation of percentage of ambiguous calls with clonal within-patient diversity at the nucleotide level Correlation between percentage ambiguous calls across all D-PCR patients by nucleotide position and within-patient diversity computed from the average metric entropy by nucleotide position from patients for which we have multiple sequences. To show detail, both axes are plotted on a log scale.

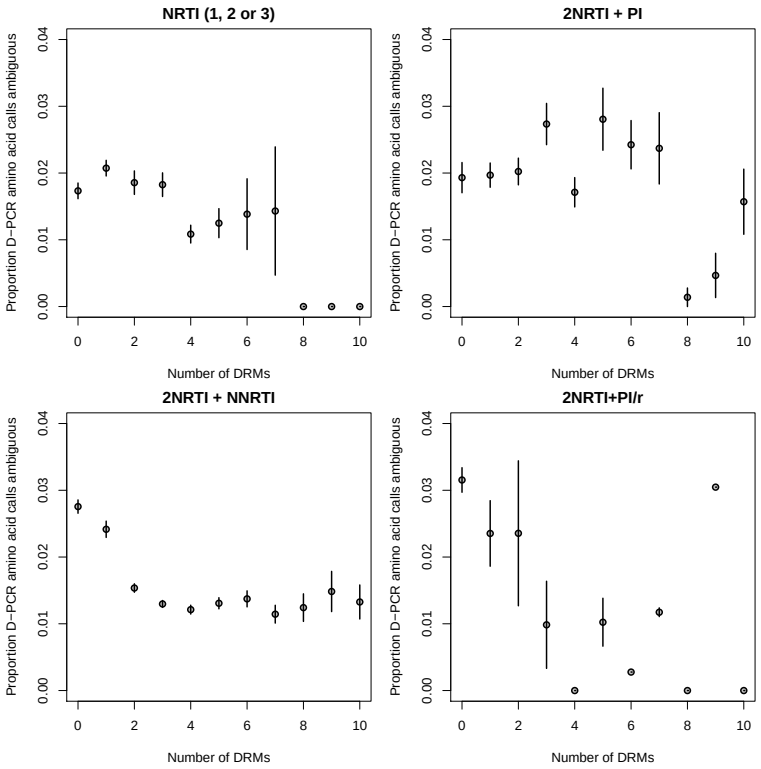

Figure 3: Diversity and the number of drug resistance mutations by treatment categories. The relationship between diversity and the number of drug resistance mutations is plotted separated out by the major treatments included in our analysis: **(A)** NRTI(s) without any other drugs, **(B)** NRTIs with unboosted PI, **(C)** NRTIs and an NNRTI and **(D)** NRTIs and PI/r. Data plotted is just the abundant treatment dataset.

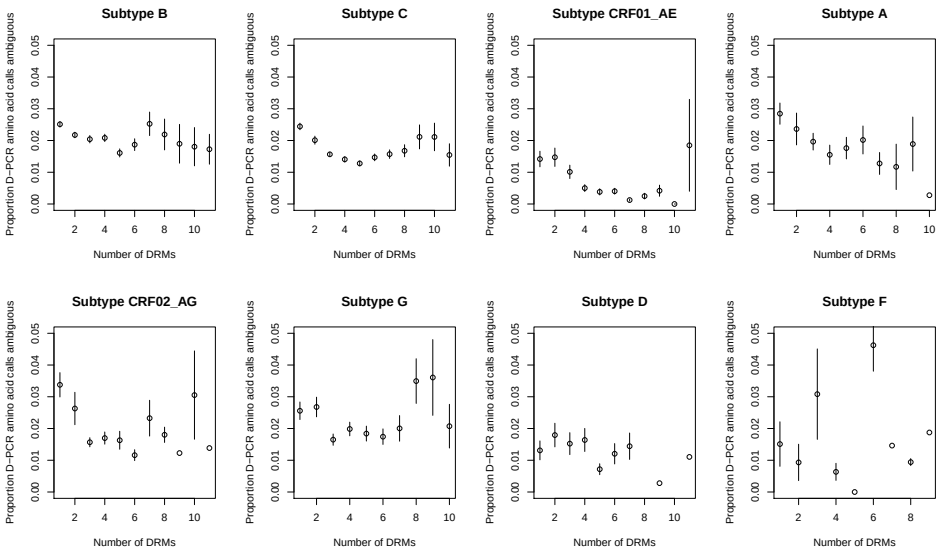

Figure 4: Effect of multiple DRMs on sequence diversity separated by subtype Average diversity level of sequences are plotted conditioned on number of fixed drug resistance mutations present separately by all the subtypes with more than 100 associated HIV populations. Means $\pm$ SE are plotted among all the D-PCR dataset.

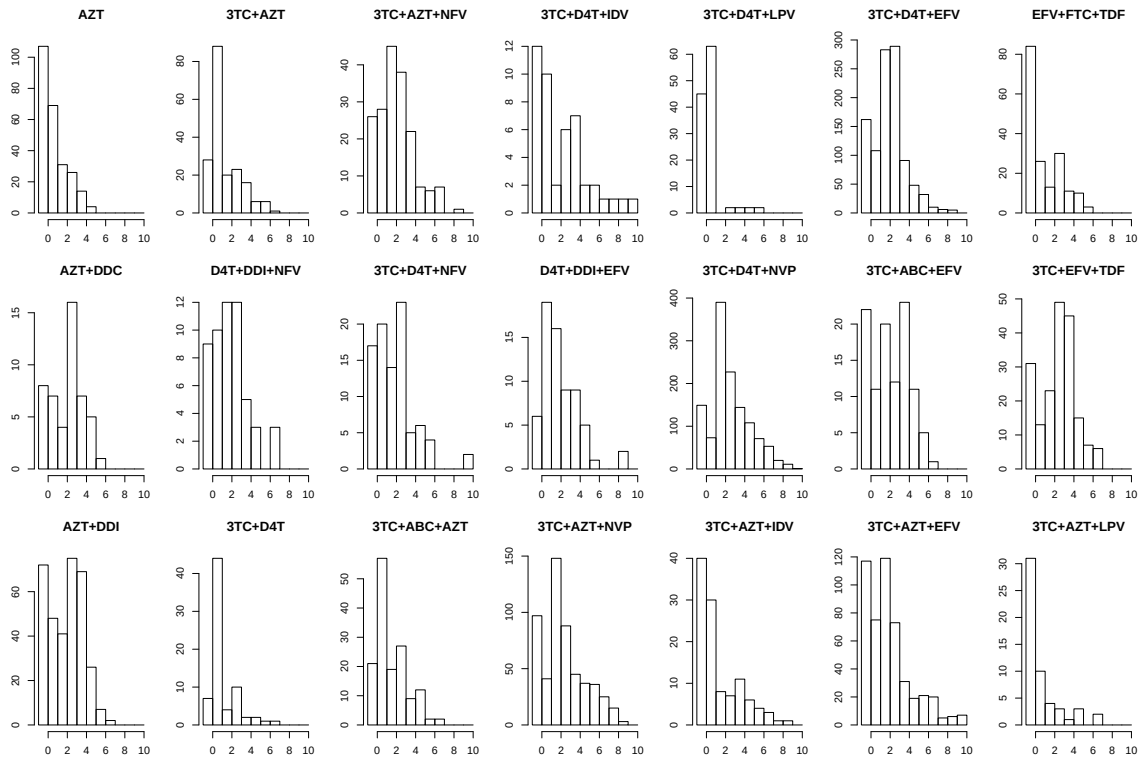

Figure 5: Distribution of number of DRMs by treatment The distribution of the number of drug resistance mutations is plotted separated out by the major treatments included in our analysis. The y-axes are not standardized, and show the number of consensus sequences per treatment with each number of fixed DRMs within the well-defined dataset.

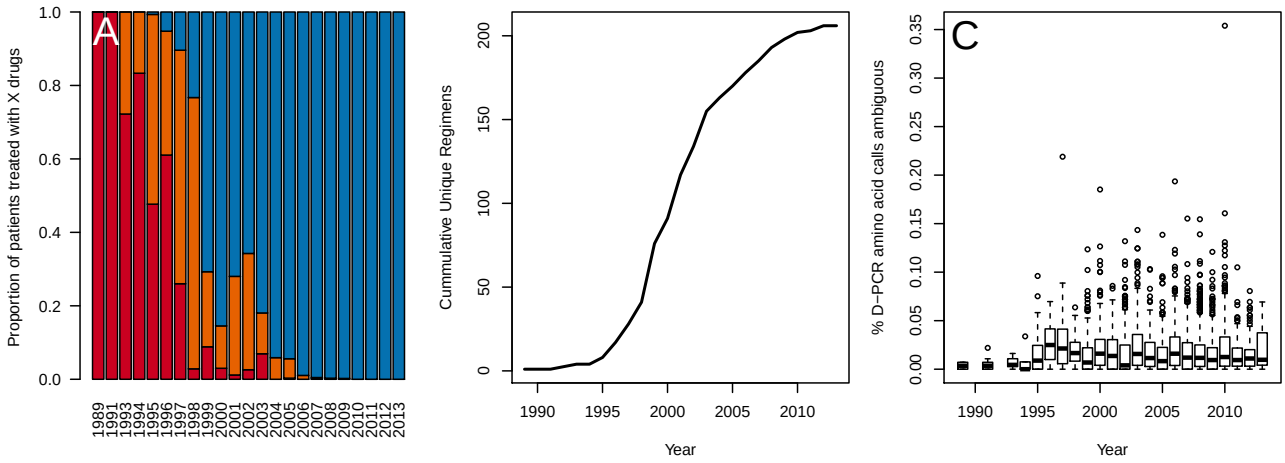

Figure 6: Data is heterogenous with respect to year (A) Percentage of patients receiving 1, 2 or 3 or more drugs (red, orange and blue bars, respectively) changes over the timecourse of our sampling period. **(B)** The cummulative number of unique treatment regimens is shown over the course of our sample period. **(C)** Barplots demonstrating the number of ambiguous amino acids per amino acid position by year with interquartile ranges.

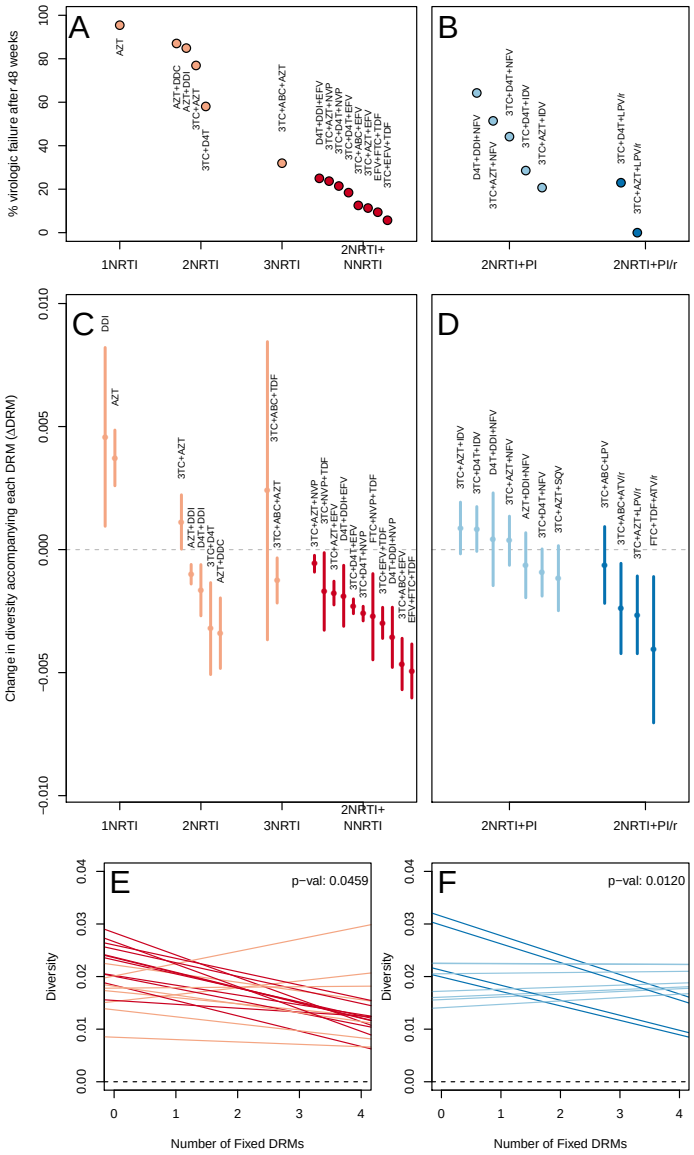

Figure 7: Drug resistance mutations are correlated with diversity reduction differently in different types of treatments with un-truncated data. Treatment efficacy from literature review (% of patients with virologic suppression after 48 weeks) showed positive correspondence with clinical recommendation among RTI regimens (A) and PI+RTI regimens (B). $\Delta_{DRM} \pm$ SE lower among the more efficacious and clinically recommended treatments among RTI treatments (C) and RTI+PI treatments (D). Mixed effect model shows significantly different slopes for NNRTI treatments versus NRTI treatments (E) and PI/r treatments versus PI treatments (F). Each line in (EF) represents the fitted decay in diversity with each DRM for a different treatment from the mixed effects model. This figure is analogous with Figure 5 from the main text, but in this case, the data is not truncated to only include the patients with 4 or fewer DRMs.

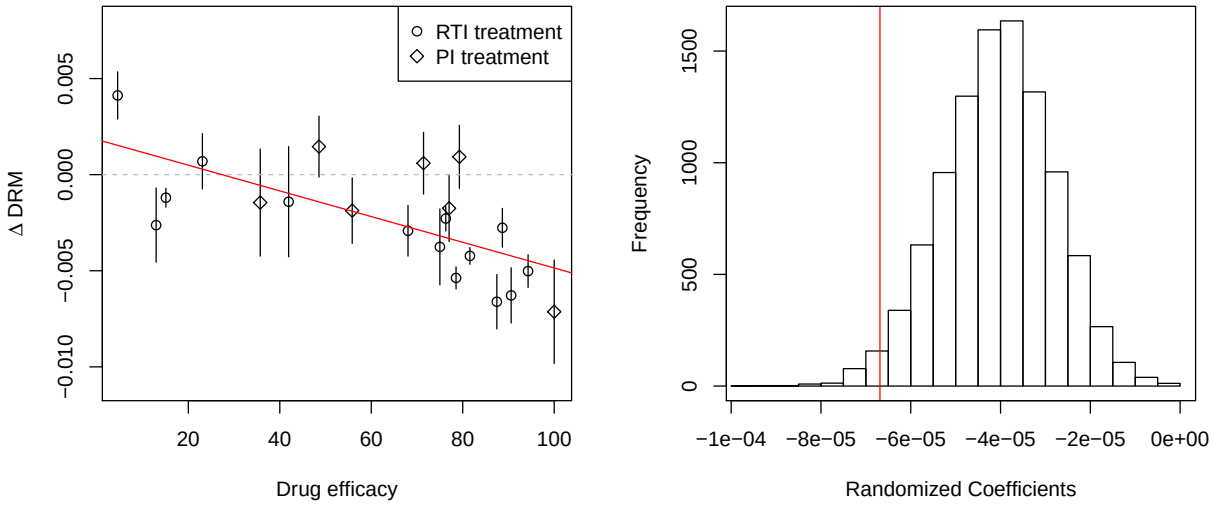

Figure 8: Nonparametric test shows negative correlation between treatment efficacy and Δ_{DRM}. Treatment efficacy from literature review (% of patients with virologic suppression after $\tilde{4}8$ weeks) showed positive correspondence with clinical recommendation among RTI regimens (A) and PI+RTI regimens (B).$\Delta_{DRM} \pm$ SE lower among the more efficacious and clinically recommended treatments among RTI treatments (C) and RTI+PI treatments (D). Mixed effect model shows significantly different slopes for NNRTI treatments versus NRTI treatments (E) and PI/r treatments versus PI treatments (F). Each line in (EF) represents the fitted decay in diversity with each DRM for a different treatment from the mixed effects model. This figure is analogous with Figure 5 from the main text, but in this case, the data is not truncated to only include the patients with 4 or fewer DRMs.

Table 1: Fixed effect coefficients from mixed effects models with and without efficacious treatment slopes Model fits for the mixed effects and null models for RTI treatments (NRTI(s) versus 2 NRTIs + NNRTI), above, and PI treatments (2NRTIs + PI versus 2NRTIs + PI/r). See *Materials and methods: model fitting* for explanations of coefficients.

RTI treatments	Δ_{all}	α_{all}	Δ_{NNRTI}	α_{NNRTI}	γ (Year)
Full model	-1.11×10^{-4}	1.95×10^{-2}	-4.35×10^{-3}	5.03×10^{-3}	1.77×10^{-4}
	(7.50×10^{-4})	(3.21×10^{-3})	(9.50×10^{-4})	(4.10×10^{-3})	(1.22×10^{-4})
Null model	-2.93×10^{-3}	2.33×10^{-2}	-	-	1.32×10^{-2}
	(1.21×10^{-4})	(2.80×10^{-3})	-	-	(1.25×10^{-3})
PI treatments	Δ_{all}	α_{all}	$\Delta_{PI/r}$	$\alpha_{PI/r}$	γ (Year)
Full model	5.59×10^{-4}	1.61×10^{-2}	-6.71×10^{-3}	9.22×10^{-3}	3.18×10^{-4}
	(8.18×10^{-4})	(5.18×10^{-3})	(2.12×10^{-3})	(4.13×10^{-3})	$3.99 \times 10^{-4})$
Null model	-7.53×10^{-4}	1.88×10^{-2}	-	-	3.82×10^{-4}
	(8.54×10^{-4})	(5.37×10^{-3})	-	-	(3.52×10^{-4})

1 Determining Treatment Efficacy

This section notes the details of how the treatment efficacies were calculated from a literature review. As we wished our treatment efficacy to represent the proportion of patients who had a treatment failure after 48 or 52 weeks, we used on-treatment analysis wherever possible. Patients who died or progressed to AIDS while on the treatment were considered treatment failures for our analysis, however patients who discontinued treatment due to rash or other adverse affects were excluded, wherever possible.

Study name: 2NN 1432 patients were randomized to 3TC+D4T+EFV, 3TC+D4T+NVP (once or twice daily) or 3TC+D4T+EFV+NVP.

3TC+D4T+EFV: 381 started treatment as allocated and 337 completed week 48. Of those that did not complete treatment, 6 died, so they were counted as treatment failures. Of the 337 who completed treatment, 280 had viral load below 50 copies/mL at 48 weeks. The treatment efficacy was recorded as 280/343.

3TC+D4T+NVP: NVP was given at two doses, but since no dose information was available in our study, the doses were combined. For once daily, 208 patients started treatment and 182 completed week 48. Of those patients, 6 died. Of the patients that completed treatment, 154 had plasma RNA concentration $<$ 50 copies/mL at week 48, resulting in a final count of 154/188. For twice daily, 378 patients started treatment and 322 completed week 48. Of those patients, 9 died. Among patients who completed week 48, 253 had Plasma RNA concentration below 50 copies/mL. Therefore, the final efficacy among the twice daily NVP group was 253/331. The combined once and twice daily efficacy was recorded as 407/529.

Study name: ABCDE 277 patients were randomized to 3TC+ABC+EFV or 3TC+D4T+EFV.

3TC+ABC+EFV: Of the that 115 started treatment, 1 died, and 1 switched because of virologic failure. These were both counted as failures. 75 patients completed the study. After 96 weeks, the ITT analysis gave 60.9% of patients with an HIV-1 RNA level $<$50 copies/mL, suggesting that 70 patients had plasma RNA levels below the threshold. The efficacy was recorded 70/77.

3TC+D4T+EFV: Of the 122 that started treatment, 1 switched out because of virologic failure and was counted as a failure, and 63 completed the study. After 96 weeks, the ITT analysis reported 47.5% of patients with a HIV-1 RNA level below the threshold, resulting in 58 successful patients. The efficacy was recorded as 58/64.

Study name: ACTG 384 620 patients were randomized to 3TC+AZT+EFV, 3TC+AZT+NFV, D4T+DDI+EFV or D4T+DDI+NFV. Patients were evaluated at two endpoints, but we considered only the first one. Virologic failure was defined as an HIV-1 RNA level above 200 copies/mL after two previous timepoints below 200 copies, an insufficient decrease (by less than a factor of 10) in RNA levels by week 8 or an increase by a factor of more than 10 above nadir measurement. The median initial followup timepoint was 28 weeks.

3TC+AZT+EFV: 155 patients started treatment. Of those patients, 30 had a premature discontinuation and 11 had a

toxicity related failure. Both groups were excluded giving a sample size of 114. 20 had a virologic failure, resulting in an efficacy measurement of 94/114.

3TC+AZT+NFV: 155 patients started treatment. Of those patients, 25 had a premature discontinuation and 3 had a toxicity related failure. Both groups were excluded giving a sample size of 127. 63 had a virologic failure, resulting in an efficacy measurement of 61/127.

D4T+DDI+EFV: 155 patients started treatment. Of those patients, 26 had a premature discontinuation and 20 had a toxicity related failure. Both groups were excluded giving a sample size of 109. 49 had a virologic failure, resulting in an efficacy measurement of 60/109.

D4T+DDI+NFV: 155 patients started treatment. Of those patients, 29 had a premature discontinuation and 19 had a toxicity related failure. Both groups were excluded giving a sample size of 107. 58 had a virologic failure, resulting in an efficacy measurement of 49/107.

Study name: ACTG A5202 1857 patients were randomized to receive 3TC+ABC+EFV, 3TC+ABC+ATV/r, EFV+FTC+TDF or ATV/r+FTC+TDF with a median followup time of 138 weeks. Virologic failure was considered as having greater RNA concentration than 200 copies/mL.

3TC+ABC+EFV: 461 patients were assigned treatment and 275 completed treatment. Of those patients that did not complete treatment, 4 died and 35 had site-declared virologic failures. Of those that finished treatment, there were 72 occurrences of virologic failure. The recorded efficacy was 203/314.

EFV+FTC+TDF: 461 patients were assigned treatment and 319 completed treatment. Of those patients that did not complete treatment, 3 died and 28 had site-declared virologic failures. Of those that finished treatment, there were 57 occurrences of virologic failure. The recorded efficacy was 262/350.

ATV +FTC+RTV+TDF: 465 were assigned treatment and 320 completed treatment. Of the patients that did not complete treatment, 3 died and 3 had site-declared virologic failure. Of those that finished treatment, there were 57 events of virologic failure. The recorded efficacy was 263/326. 3TC+ABC+ATV+RTV: 463 were assigned treatment and 338 completed treatment. Of the patients that did not complete treatment, 5 died and 11 had site-declared virologic failure. Of those that finished treatment, there were 83 events of virologic failure. The recorded efficacy was 255/354.

Study name: Advanced HIV Mexico 264 patients were assigned either LPV/r or EFV with AZT and 3TC.

3TC+AZT+EFV: 95 patients were assigned to treatment, with 80 completing the treatment of 48 weeks. Of those patients, 67 had HIV-RNA concentrations of < 50 copies/mL. Therefore, the efficacy was recorded as 67/80.

Study name: Advanz 76 patients were randomized to EFV or IDV and both 3TC and AZT and followed for 36 months.

3TC+AZT+EFV: 34 patients initially received EFV and 27 finished treatment. Of the 7 who did not finish, 4 died and

were considered failures. 63% (17) of on treatment patients met the success endpoint of <50 copies/mL. The efficacy was recorded as 17/31.

3TC+AZT+IDV: 31 patients initially received IDV and 18 finished treatment. Among the 13 who did not finish, 1 died. 44% (8) of on treatment patients met the success endpoint of <50 copies/mL. The efficacy was recorded as 8/19.

Study name: AI424-007

420 patients were randomized to either one of three doses of ATV or NFV, with D4T and DDI.

D4T+DDI+NFV: 100 patients were treated with NFV. 84 patients completed 48 weeks, and no discontinuities clearly indicating virologic failures. 32 patients had plasma HIV-RNA levels below 50 copies/mL after 48 weeks, resulting in an efficacy of 32/84.

Study name: AI424-008 467 patients were randomized to either ATV or NFV, with 3TC and D4T.

3TC+D4T+NFV: 91 patients were assigned treatment, and 80 completed 48 weeks. Of those that did not, 3 were discontinued for lack of efficacy/disease progression, and were considered failures. 31 of the patients that completed treatment had HIV-1 RNA $<$ 50 copies/mL. The efficacy was recorded as 31/83.

Study name: AI454-148 756 patients were randomized to either D4T+DDI+NFV or 3TC+AZT+NFV and virologic response after 48 weeks was measured (two consecutive viral loads <50 copes/mL maintained to 48 weeks).

D4T+DDI+NFV: 503 patients were assigned treatment and 171 (34%) achieved a virologic response. 14 patients were excluded for various reasons and were not counted as part of the population. The recorded efficacy was 171/489.

3TC+AZT+NFV: 253 patients were assigned treatment and 119 (47%) achieved a virologic response. 8 patients were excluded for various reasons, and were not counted as part of the population. The recorded efficacy was 119/245.

Study name: AI454-152 511 patients were randomized to either 3TC+AZT+NFV or D4T+DDI+NFV and were followed for 48 weeks/

3TC+AZT+NFV

D4T+DDI+NFV Insufficient information to do anything beyond a ITT analysis

Study name: Altair 422 patients were randomized to receive EFV+FTC+TDF or other treatments. Patients were followed up after 48 weeks.

EFV+FTC+TDF: 114 patients were treated and 111 remained on the study for 48 weeks. Two of the patients who stopped treatment died of causes unrelated to HIV. Of the patients that completed the study, 82 patients had HIV-RNA levels <50 copies/mL. The study lists the per protocol population 82 successes as 93%, suggesting a per protocol population size of

88, although it was unclear how this number was reached. The efficacy used was 82/88.

Study name: ARES 71 patients were randomized to receive D4T+DDI+NFV, 3TC+DDI+NVP or other treatments and were followed for 48 weeks.

D4T+DDI+NFV: 26 patients received treatment, and 42.6% had <50 copies HIV-RNA/mL, or 11 patients. Although the remaining 15 patients switched treatments, it is not clear when these events happened. The efficacy was recorded as 11/26.

3TC+DDI+NVP: 22 patients received treatment, and 50% had <50 copies HIV-RNA/mL, or 11 patients. Although the remaining 11 patients switched treatments, it is not clear when these events happened. The efficacy was recorded as 11/22.

Study name: AVANTI 2 103 patients were randomized to receive 3TC+AZT or 3TC+AZT+IDV.

3TC+AZT+IDV: 52 were assigned to treatment, and 39 finished the study. 9 of these patients had HIV-1 RNA levels < 500 copies/ml and 2 had HIV-1 RNA levels < 20 copies/mL. The efficacy was recorded as 2/39.

3TC+AZT: 51 were assigned to treatment, and 40 finished the study. 31 of these patients had HIV-1 RNA levels < 500 copies/ml and 24 had HIV-1 RNA levels < 20 copies/mL. The efficacy was reported as 24/40.

Study name: BMS-001 204 patients were randomized to receive 3TC+AZT+IDV or 3TC+D4T+IDV .

3TC+AZT+IDV: 103 patients were assigned to treatment and 65 completed the 48 week study period. Of the patients that dropped out, 1 had major disease progression, and was considered a treatment failure. There was also a death unrelated to HIV that was not counted as a treatment failure. Of the treated patients, 73% (48 patients) achieved viral load below 50 HIV-RNA copies/mL, resulting in a efficacy of 48/66.

3TC+D4T+IDV: 101 patients were assigned to treatment and 87 completed the 48 week study period. None of the treatment drop outs were indicated to be due to death, disease progression or virologic failure. Of the treated patients, 85% (74 patients) achieved viral load below 50 HIV-RNA copies/mL, resulting in a efficacy of 74/87.

Study name: BMS-002 205 patients were randomized to receive 3TC+AZT+IDV or D4T+DDI+IDV and were monitored for 48 weeks.

3TC+AZT+IDV: 103 patients received treatment and 58 completed treatment. Of the patients that did not complete treatment, one had an increasing viral load and was considered a treatment failure. Of the patients that did finish treatment, 70% of 52 patients (36) had HIV-RNA levels below 50 copies/mL. Therefore, the treatment efficacy was recorded as 36/53.

Study name: CCTG589 51 patients were randomized to receive EFV+FTC+TDF or other treatment and were followed for 48 weeks.

EFV+FTC+TDF: 25 were assigned treatment, and 23 completed treatment. Of the patients that did not complete treat-

ment, neither died or suffered virologic failure. After 48 weeks, 88% achieved an HIV RNA level < 50 copies/mL. The efficacy was recorded as 23/25.

Study name: Chelsea Westminster 114 individuals were randomized to receive 3TC+AZT+EFV or other medication and were monitored for 48 weeks.

3TC+AZT+EFV: 56 patients were assigned treatment and 40 patients finished 48 weeks. Of the patients that discontinued the study, no patients had virologic failure or death. Among the patients on treatment, 40 of 40 patients had HIV-RNA < 50 copies/mL. The efficacy was recorded as 40/40.

Study name: CNA109586 (ASSERT) 392 patients were randomized to receive 3TC+ABC+EFV or EFV+FTC+TDF and were monitored for 48 weeks.

3TC+ABC+EFV: 192 patients were given treatment and 129 completed week 48. Of the patients who discontinued study, 1 had disease progression, 4 had insufficient viral load response, and 7 had virologic failure. These 12 patients were considered treatment failure. Of the 129 that completed treatment, 114 achieved HIV-RNA levels < 50 copies/mL. The final efficacy for the treatment was recorded as 114/141.

EFV+FTC+TDF: 193 patients were given treatment and 149 completed wek 48. Of the patients who discontinued the study, 2 had insufficient viral load response and were considered failures. Of the 149 that completed treatment, 137 achieved HIV-1 RNA levels < 50 copies/mL. The treatment efficacy was recorded as 137/151.

Study name: CNA30024 649 patients were randomized to receive either 3TC+ABC+EFV or 3TC+AZT+EFV and were followed for 48 weeks.

3TC+ABC+EFV: 324 patients began treatment and 253 completed treatment for 48 weeks. Of those that did not complete treatment, 2 had disease progression and 2 had insufficient viral load response, resulting in 4 additional counted treatment failures. The intention to treat analysis reports that approximately 70% of patients had viral load < 50 copies/mL after 48 weeks, or approximately 227 patients. The recorded treatment efficacy was 227/257.

3TC+AZT+EFV: 325 patients began treatment, and 250 completed treatment for 48 weeks. Of those that did not complete treatment, 1 had disease progression and 2 had insufficient viral load responses, resulting in an additional 3 counted treatment failures. The intention to treat analysis reports that approximately 68% of patients had viral load < 50 copies/mL after 48 weeks, or approximately 221 patients. The recorded treatment efficacy was 221/253.

Study name: CNAAB3005 562 patients were randomized to either receive 3TC+ABC+AZT or 3TC+AZT+IDV

3TC+ABC+AZT: 262 patients received treatment and 160 completed the study after 48 weeks. Of the patients who discontinued treatment, 3 died and 4 had virologic failure. Because 2 deaths were unrelated to treatment, an additional 5

treatment failures were added. The as-treated analysis suggests only 150 patients completed the study, and that 70% of those patients had HIV-1 RNA levels <50 copies/mL but the discrepancy between the number who received treatment and the number in the as-treated analysis is not clear. This would imply that 105 patients achieved sufficiently low viral load. We recorded the efficacy with respect to the given as treatment analysis, including the other 5 categorized failures, for a final efficacy of 105/155.

3TC+AZT+IDV: 265 patients received treatment and 156 completed the study after 48 weeks. Of the patients who discontinued treatment, 1 died of unrelated causes and 3 had virologic failure, adding an additional 3 treatment failures. The as-treated analysis suggests only 148 patients completed the study, and that 82% of those patients had HIV-1 RNA levels <50 copies/mL but the discrepancy between the number who received treatment and the number in the as-treated analysis is not clear, despite the study noting two missing plasma samples. This would imply that 121 patients achieved sufficiently low viral load. We recorded the efficacy with respect to the given as treatment analysis, including the other 3 categorized failures, for a final efficacy of 121/151.

Study name: CNAB3014 329 patients were randomized to receive 3TC+ABC+AZT or 3TC+AZT+IDV and were followed for 48 weeks.

3TC+ABC+AZT: 164 patients were randomized to receive treatment and 129 completed the study after 48 weeks. Among the patients that discontinued treatment, none of them were due to insufficient virologic response, death or other clear indications of virologic failure. 126 patients were eventually used in the as treated analysis, and regarded as the full sample. Of the 126 patients, 99 achieved HIV-RNA levels < 50 copies/mL after 48 weeks The treatment efficacy was recorded as 99/126.

3TC+AZT+IDV: 165 patients were randomized to receive treatment and 103 finished the study after 48 weeks. Among the patients that discontinued treatment, none of them were due to insufficient virologic response, death or other clear indications of virologic failure. 101 patients were eventually used in the as treated analysis, and regarded as the full sample. Of the 101 patients, 82 achieved HIV-RNA levels < 50 copies/mL after 48 weeks. The treatment efficacy was recorded as 82/101.

Study name: DMP 266-006 450 patients were randomized to receive 3TC+AZT+EFV or 3TC+AZT+IDV and monitored for 48 weeks. 10 patients were excluded because of lack of virologic response, but it was not possible to determine the proportions corresponding to each treatment.

3TC+AZT+EFV: 154 patients were assigned treatment and 27% of patients discontinued treatment for any reason, suggesting that 108 patients finished the treatment regimen. The on-treatment analysis lists 103 patients as having finished the 48th week, but the discrepancy between the two numbers is not clearly stated. Of these, 90% (93 patients) had HIV RNA level < 50 copies/mL. The final recorded efficacy was 93/103.

3TC+AZT+IDV: 148 patients were assigned treatment and 43% patients discontinued treatment for any reason, suggesting that 84 patients finished the treatment regimen. The on-treatment analysis lists 80 patients as having finished the 48th

week, but the discrepancy between the two numbers is not clearly stated. Of these, 79% (63 patients) had HIV RNA level $<$ 50 copies/mL. The final recorded efficacy was 63/80.

Study name: EARTH 2 94 patients were assigned to 3TC+D4T+IDV, AZT+3TC or 3TC+D4T and a follow-up was performed after 52 weeks.

3TC+D4T+IDV: 32 patients were assigned to treatment and 3 were lost to follow-up resulting in 29 patients finishing treatment. 27 of these patients had viral load lower than 200 copies/mL, resulting in an overall efficacy reported of 27/29.

AZT+3TC: 28 patients were assigned to treatment and 4 were lost to follow-up resulting in 24 patients finishing treatment. 8 of these patients had viral load lower than 200 copies/mL, resulting in an overall efficacy reported of 8/24.

3TC+D4T: 34 patients were assigned to treatment and 3 were lost to follow-up resulting in 31 patients finishing treatment. 13 of these patients had viral load lower than 200 copies/mL, resulting in an overall efficacy reported of 13/31.

Study name: EPV20001 554 patients were randomized to 3TC+AZT+EFV, with 3TC either once or twice daily. Because our data did not include any information about dosage, we combined these two studies together.

3TC+AZT+EFV: 554 patients were started on treatment, of which 379 finished treatment after 48 weeks. Of the patients who discontinued study treatment, 14 had a virologic failure, and were counted as failures. 360 were included in the on treatment analysis after 48 weeks, but the discrepancy between the amounts of patients in the on-treatment analysis and the discontinued patients was not clear. 333 patients had plasma HIV-1 RNA levels $<$ 50 copies/mL after 48 weeks. The treatment efficacy was recorded as 333/374.

Study name: EPZ104057 (HEAT) 694 patients were randomized to either 3TC+ABC+LPV or FTC+LPV+TDF and followed 96 weeks.

3TC+ABC+LPV: 343 patients were treated and 234 completed week 96. Among the patients that discontinued treatment, 8 experienced protocol defined virologic failure and were counted as treatment failures. At week 96. 63% of 188 patients and 56% of 155 patients had achieved viral load $<$ 50 copies/mL, for a total of approximately 205 patients. The recorded treatment efficacy was 205/242.

FTC+LPV+TDF: 345 patients received treatment and 221 completed the study through week 96. Among the patients that discontinued treatment, 6 experienced protocol-defined virologic failure and 1 experienced disease progression. These 7 patients were counted as treatment failures. At week 96. 58% of 205 patients and 58% of 140 patients had achieved viral load $<$ 50 copies/mL, for a total of approximately 200 patients. The recorded treatment efficacy was 200/228.

Study name: ESS100327 (ACTION) Patients were randomized to either 3TC+ABC+AZT or 3TC+ATV+AZT and were followed for 48 weeks.

3TC+ABC+AZT: 138 patients were assigned to treatment, and 103 completed week 48. Of the patients that did not complete treatment, 9 were virologic failures and were considered treatment failures. 62% of intention to treat patients had HIV-1 RNA levels $<$ 50 copies/mL after 48 weeks, or approximately 86. The treatment efficacy recorded was 86/112.

Study name: ESS100732 (KLEAN) 887 patients were randomized to receive either 3TC+ABC+LPV or other treatment. They were then followed for 48 weeks.

3TC+ABC+LPV: 444 started treatment, and 345 completed treatment at week 48. Of the patients who did not complete treatment, 6 were protocol-defined virological failures. 288 patients achieved HIV-RNA levels $<$ 50 copies/mL after 48 weeks. The recorded treatment efficacy was 288/351.

Study name: ESS30009 340 patients were randomized to receive either 3TC+ABC+EFV or 3TC+ABC+TDF and were monitored for 48 weeks.

3TC+ABC+EFV: 169 were treated and 127 finished treatment at week 48. Among the patients that were discontinued from treatment, 3 had a virologic failure. 120 patients achieved HIV RNA levels $<$50 copies/mL after 48 weeks. The treatment efficacy was recorded as 120/130.

3TC+ABC+TDF: 171 were treated, and 113 remained in the study at week 48. Among the patients that stopped treatment, 6 had a virologic failure. The proportion of virologic nonresponse was sufficiently high that the program was drastically modified for many patients. The proportion of patients with suppressed viral load after 48 weeks was not reported.

Study name: ESS40001 (CLASS) 291 patients were randomized to receive 3TC+ABC+D4T, 3TC+ABC+EFV or other treatment and were followed for 96 weeks.

3TC+ABC+D4T: 98 patients started treatment and 27 stopped assigned treatment prematurely with 9 of those patients stopping for virologic reasons. 71 patients were recorded to have finished their treatment, with an additional 9 failures. 61% of 98 (60) achieved viral load $<$ 50 copies/mL. The recorded efficacy was 60/80.

3TC+ABC+EFV: 97 patients started treated and 24 patients stopped assigned treatment prematurely, although none because of specifically stated virologic reasons. 68% of 97 (73) patients ended treatment. 65 patients achieved viral load $<$ 50 copies/mL. The final recorded efficacy was 65/73.

Study name: ESS40002 254 patients were randomized to receive 3TC+ABC+AZT, 3TC+AZT+NFV, or 3TC+D4T+NFV and were monitored for 96 weeks.

3TC+ABC+AZT: 87 patients were assigned to treatment, and 46 completed 96 week trial. Of the patients that discontinued study, 6 were virologic failures and were considered treatment failures. 35 patients achieved HIV RNA levels of $<$ 50 copies/mL. The recorded efficacy was 35/52.

3TC+AZT+NFV: 91 patients were assigned to treatment, and 43 completed 96 week trial. Of the patients that discontinued study, 14 were virologic failures and were considered treatment failures. 34 patients achieved HIV RNA levels of < 50 copies/mL. The recorded efficacy was 34/57.

3TC+D4T+NFV: 83 patients were assigned to treatment, and 43 completed 96 week trial. Of the patients that discontinued study, 8 were virologic failures and were considered treatment failures. 27 patients achieved HIV RNA levels of < 50 copies/mL. The recorded efficacy was 27/51.

Study name: FTC301A 580 patients were randomized to receive treatment and were followed for 48 weeks.

D4T+DDI+EFV: 285 received treatment, and 193 completed the study after 48 weeks. Of the patients that discontinued the study, 1 died, and 30 suffered virological failure. At week 48, 59% of patients (168) had achieved and maintained a viral load of $<$50 copies/mL. The treatment efficacy was recorded as 168/224.

DDI+EFV+FTC: 286 received treatment and 232 completed the study after 48 weeks. Of the patients that discontinued the study, 10 suffered virological failure and were counted as treatment failures. 78% of patients (181) had achieved and maintained a viral load of $<$50 copies/mL at week 48. The treatment efficacy was recorded as 181/242.

Study name: GESIDA 3093 376 patients were randomized to treatment and were followed for 48 weeks.

3TC+DDI+EFV: 186 patients were treated and 147 finished the study at week 48. Of the patients that discontinued treatment, 1 died and 6 suffered virologic failure. These 7 patients were treated as treatment failures. 88% (129) of on treatment patients achieved HIV RNA levels < 50 copies/mL at week 48, and the treatment efficacy was recorded as 129/154.

3TC+AZT+EFV: 183 patients started treatment, and 129 finished the study at week 48. Of the patients that discontinued treatment, 3 died and 1 suffered virologic failure. 89% of on treatment patients achieved HIV RNA levels < 50 copies/mL at week 48, and the treatment efficacy was recorded as 115/133.

Study name: GS-01-934 463 patients were randomized to receive treatment and followed for 96 weeks.

3TC+AZT+EFV: 231 patients received treatment. Of those patients, 140 achieved viral load < 50 copies/mL of the 143 patients who completed the study. 12 patients had virologic rebound and 2 died and were counted as failures. All other study participants withdrew for reasons that were not specified as virologic. The recorded treatment efficacy was 140/157.

EFV+FTC+TDF: 232 patients received treatment. Of those patients, 155 achieved viral load < 50 copies/mL of the 173 that completed the study. 2 patients had virologic rebound and 2 died and were counted as failures. All other study participants withdrew for reasons that were not specified as virologic. The recorded treatment efficacy was 155/177.

Study name: GS-99-903 753 patients were randomized to receive treatment and were monitored for 144 weeks.

3TC+EFV+TDF: 299 were treated and 217 completed the study. Of the patients who did not complete the study, 10 had

suboptimal virologic response, and 1 died, resulting in an additional 11 treatment failures. After 144 weeks, 203 patients had viral load $<$ 50 copies/mL. The recorded treatment efficacy was 203/228.

3TC+D4T+EFV: 301 were treated and 201 completed the study. Of the patients who did not complete the study, 5 had suboptimal virologic response and 3 died, resulting in an additional 8 treatment failures. After 144 weeks, 188 patients had viral load $<$ 50 copies/mL. The recorded treatment efficacy was 188/209.

Study name: GS-US-236-0102 707 patients were randomized to receive treatment and were monitored for 48 weeks.

EFV+FTC+TDF: 352 patients were treated and 306 remained on the study drug at week 48. Of the patients that discontinued treatment, 4 withdrew because of lack of efficacy and 1 died, resulting in an additional 5 failures. After 48 weeks, 288 patients achieved a viral load of $<$ 50 copies/mL. The efficacy recorded was 288/311.

Study name: GS-US-236-0104 71 patients were randomized to receive treatment and were monitored for 48 weeks.

EFV+FTC+TDF: 23 patients received treatment and 3 patients did not finish treatment. After 48 weeks, 19 patients achieved HIV RNA levels $<$ 50 copies/mL. The efficacy was recorded as 19/20.

Study name: GS-US-264-0110 784 patients were randomized to receive treatment and were monitored for 48 weeks.

EFV+FTC+TDF: 392 patients received treatment. 6% discontinued due to virologic related reasons (23 patients) and were counted as failures. 8% (31 patients) discontinued due to non-virologic reasons and were excluded from the efficacy calculation. 81% of patients (317) achieved HIV RNA levels $<$ 50 copies/mL. The efficacy was recorded as 317/361.

FTC+TDF+RPV: 392 patients received treatment. 2% (8 patients) discontinued due to non-virologic reasons and were excluded from the analysis. 86% of patients (337) achieved HIV RNA levels $<$ 50 copies/mL. The efficacy was recorded as 337/384.

Study name: LAKE 126 patients were randomized to receive treatment and were monitored for 48 weeks

3TC+ABC+EFV: 63 patients were treated and 45 completed the study. Of the patients who did not, 1 suffered virologic failure. After 48 weeks, 92% of patients (41) had achieved HIV RNA levels $<$ 50 copies/mL. The recorded treatment efficacy was 41/46.

3TC+ABC+LPV: 63 patients were treated and 40 completed the study. Of the patients who did not, 1 suffered virologic failure. After 48 weeks, 92.3% of patients (37) had achieved HIV RNA levels $<$ 50 copies/mL. The recorded treatment efficacy was 37/41.

Study name: LORAN 75 patients were randomized to treatment and monitored for 48 weeks.

3TC+AZT+LPV: 35 patients were assigned treatment. After 48 weeks, 29 of 29 patients had achieved HIV RNA < 50 copies/mL. No patients were discontinued because of virologic failure in this arm, so the final recorded efficacy was 29/29.

Study name: M98-863 653 patients were randomized to treatment and monitored for 48 weeks

3TC+D4T+NFV: 326 were treated and 270 completed treatment. Among the patients who discontinued treatment, 2 were virologic failure and 5 died, so an additional 7 patients were counted as treatment failures. Intention to treat analysis suggests that 52% of patients (170) achieved viral load of < 50 copies/mL after 48 weeks. The recorded efficacy for the treatment was 170/277.

3TC+D4T+LPV: 327 were treated and 250 completed treatment. Of the patients who discontinued treatment, 30 suffered virologic failure and 3 died, so an additional 33 cases were counted as treatment failures. Intention to treat analysis suggests that 67% of patients (219) achieved viral load of < 50 copies/mL after 48 weeks. The recorded efficacy for the treatment was 219/288.

Study name: M99-056 38 patients were randomized to receive treatment either once or twice daily and monitored for 48 weeks. Because our data did not have any information about dosage, both treatment levels were combined.

3TC+D4T+LPV: 38 patients started treatment and 34 finished the study at 48 weeks with no patients being recorded as cases of virologic failure or death. 79% of 19 and 74% of 19 for a total of 29 patients had viral load < 50 copies/mL at week 48. The recorded efficacy was 29/34.

Study name: MK0518-004 201 patients were randomized to treatment and followed for 48 weeks.

3TC+EFV+TDF: 38 patients started treatment and 35 patients completed treatment at week 48. None of the 3 patients that discontinued treatment were attributed to virologic failure. 87% of patients (33) had HIV RNA < 50 copies/mL. The recorded efficacy was 33/35.

Study name: N2R 142 patients were randomized to treatment and followed for 48 weeks.

3TC+D4T+EFV: 71 patients started on treatment and 62 completed treatment. Of the patients that did not complete treatment, 2 died and were considered treatment failure. 52 patients achieved HIV RNA level < 50 copies/mL, and the final efficacy was recorded as 52/64.

3TC+D4T+NVP: 71 patients started on treatment and 55 completed treatment after 48 weeks. Of the patients that did not complete treatment, 6 died and were considered treatment failures. 51 patients achieved HIV RNA level < 50 copies/mL and the final efficacy was recorded as 51/61.

Study name: Nigerian ARV Program 50 patients were monitored over a year to determine the efficacy of NVP treatment.

3TC+D4T+NVP: 50 patients were assigned treatment. Insufficient information to determine treatment failures versus other.

Study name: RA (DART substudy) 600 patients were randomized to receive treatment and were monitored for 48 weeks

3TC+ABC+AZT: 300 patients started treatment and 283 patients finished treatment. Of the patients that did not finish treatment, 9 died. After 48 weeks, 176 patients had $<$ 50 copies/mL of HIV RNA. The recorded efficacy is 176/292.

3TC+AZT+NVP: 300 patients started treatment, and 269 completed treatment. Of the patients that did not finish treatment, 16 died and were counted as treatment failures. After 48 weeks, 207 patients had $<$ 50 copies/mL of HIV RNA. The recorded efficacy is 207/285.

Study name: NVP China 198 patients were treated for 52 weeks.

3TC+D4T+NVP: 69 patients were treated and 53 finished the study. It was not specified that any of the patients who discontinued treatment failed virologically. At 52 weeks, 68.2% of patients (47) had viral loads $<$ 50 copies/mL. The efficacy was recorded as 47/53.

3TC+AZT+NVP: 64 patients were treated and 44 finished the study. It was not specified that any of the patients who discontinued treatment failed virologically. At 52 weeks, 69% of patients (44) had viral loads $<$ 50 copies/mL. The efficacy was recorded as 44/44.

Study name: ONCE – abstract only Only the abstract was available, but on treatment analysis is reported. This assessment might be conservative, since it will not account for off treatment patients who also failed therapy by our specifications. No sample size given.

3TC+AZT+EFV 3TC+AZT+NFV

Study name: OZCOMBO 1 106 patients were randomized to receive one of three treatments and followed for 52 weeks.

3TC+AZT+IDV: 35 patients were treated, and 25 completed 52 weeks of treatment. Of the patients that did not finish treatment, one was due to treatment failure. 66% of patients (23) achieved viral load of 50 copies/mL. The recorded treatment efficacy is 23/25

3TC+D4T+IDV: 34 patients were treated and 28 completed 52 weeks of treatment. No patient who did not complete treatment had a failure that was designated as virologic. 59% of patients (20) achieved viral load of $<$ 50 copies/mL. The recorded treatment efficacy is 20/28.

Study name: OZCOMBO 2 – abstract only

3TC+AZT+NVP

3TC+D4T+NVP

Study name: QUAD 53 patients were given 3TC+AZT+EFV or a four-drug treatment and monitored for 48 weeks.

3TC+AZT+EFV: 26 patients were treated and 23 finished the treatment. None of the treatment discontinuations were due to virologic reasons. 88% of patients had viral load $<$ 50 copies/mL at week 48 (23) and the recorded efficacy was 23/23.

Study name: SENC– abstract only, insufficient information

D4T+DDI+EFV

D4T+DDI+NVP

Study name: South African Workplace HIV Program - abstract only, insufficient information

3TC+AZT+EFV

Study name: Thai Indinavir Single arm study to examine efficacy of 3TC+D4T+IDV over the course of 96 weeks. While samples were collected at 48 weeks, the efficacies reported are not available in the abstract.

3TC+D4T+IDV: 80 patients began treatment and treatment was completed in 62 patients. Of the patients that did not complete treatment, four died and were treated as treatment failures. The on treatment analysis reports that 88.7% of patients (55) achieved HIV RNA level $<$ 50 copies/mL. The recorded efficacy was 55/66.

Study name: VACH - unsure 629 patients were randomized to receive 3TC+AZT+EFV or 3TC+DDI+EFV and followed for 36 weeks.

3TC+AZT+EFV: 409 patients began treatment and 202 completed the study. Of the patients who did not complete the study, 33 have a virologic failure and 26 had an AIDS defining event or death. These 59 patients were considered treatment failures.

3TC+DDI+EFV: 219 patients began treatment and 158 completed the study. Of the patients who did not complete the study 13 had a virologic failure and 8 had an AIDS defining event or death. These 21 patients were counted as treatment failures.

Study name: CNAF3007 – paper not accessible Necessary on treatment analysis **3TC+AZT+NFV**

3TC+ABC+AZT

Study name: COMBINE – paper not accessible **3TC+AZT+NFV 3TC+AZT+NVP**

Study name: CTN 177 - no on-treatment analysis could be determined. **3TC+AZT+NVP 3TC+AZT+LPV**

Study name: Delta HIV-1 viral load, phenotype, and resistance in a subset of drug-naive participants from the Delta trial 240 patients were randomized to receive treatment and were monitored for up 96 weeks. Reasons for discontinuation were not quantified in the study, but it can be assumed that many of them were treatment failures. Towards that end, the estimates made excluding these patients from being considered failures suggests that we measure a conservative treatment efficacy.

AZT: 87 patients were treated and at the end of 48 weeks, 66 remained on treatment. At the end of 48 weeks, 5% of patients (3) were below the detection limit. The treatment efficacy recorded was 3/66.

AZT+DDI: 80 patients were treated and at the end of 48 weeks, 53 remained on treatment. At the end of 48 weeks, 15% of patients (8) were below the detection limit. The treatment efficacy recorded was 8/53.

AZT+DDC: 73 patients were treated, and at the end of 48 weeks, 54 remained on treatment. At the end of 48 weeks, 13% of patients (7) were below the detection limit. The treatment efficacy recorded was 7/54.

Study name: ATCG 175 Insufficient information to determine on-treatment analysis.

Study name: CPCRA 1102 patients were randomized to receive AZT, AZT+DDI or AZT+DDC, but many had previously received AZT. There's no viral load data.

AZT: 372 patients received treatment and of those, 157 patients died or suffered disease progression and were considered treatment failure at 12 months.

AZT+DDC: 367 patients received treatment and of those, 141 patients died or suffered disease progression and were considered treatment failure at 12 months.

Study name: Raffi et al Single arm treatment efficacy study for DDI and D4t with 64 patients **D4T+DDI**: 65 patients were assigned, and 6 dropped out by week 24 due to reasons unrelated to virological failure. 8 of the 59 had a viral load fall below detectable levels ($<$500 copies/mL) at 24 weeks. The efficacy was recorded as 8/59.

2 Table 2: Treatment Efficacy Table (all studies)

Below is a chart summarizing, for each treatment, all relevant studies and the observed number of successes (viral load less than some limit after a defined number of weeks) and the total number of patients in the study. Patients discontinuing treatment due to adverse effects (like rash) were excluded, but patients who died or progressed to AIDS were included as non-successes. Highlighted in green are study observations that were included in our final count for treatment efficacy and were considered comparable enough to take an average. In order to be consistent (and because percentage of viral suppression is not linear with respect to time), we included only studies in which patients were observed for 48-52 weeks. For most studies, we only examined included studies in which the viral load cutoff for "success" was 50 copies/mL. However, this data was not available in all cases. In a few cases (marked in blue), we included studies that had higher viral load cutoffs. This happened when: 1) the number of weeks fell within the 48-52 week range, 2) we had no other observations for treatment efficacy, and 3) we perceived the measure to be conservative. This situation arose most often for the poorer treatments with low efficacies. Because the VL limit in these cases (200-500 copies/mL) was higher than the standard 50 copies/mL, it follows that the true treatment efficacy was actually lower than we observed (i.e., if the true viral load was 100 copies/mL, these studies would mark it as a success, but it would normally be marked as a failure with the 50 copies/mL cutoff). In this way, the efficacy of these monotherapies and double therapies had their efficacy inflated, which would our observed pattern. NAs mark studies in which our desired parameterization of success could not be identified.

Treatment	Study Name	Weeks	VL limit	Successes	Total
3TC+ABC+ATV+RTV	ACTG A5202 [9]	138	200	255	354
3TC+ABC+AZT	CNAAB3005[54]	48	50	105	155
	CNAB3014[60]	48	50	99	126
	CNAF3007[33]	NA	NA		
	ESS100327 (ACTION) [27]	48	50	86	112
	RA (DART substudy) [36]	48	50	176	292
	ESS40001 (CLASS) [2]	96	50	60	80
3TC+ABC+EFV	ABCDE[42]	96	50	70	77
	ACTG A5202[9]	138	200	203	314
	CNA109586 (ASSERT)[43]	48	50	114	141
	CNA30024[10]	48	50	227	257
	ESS30009[17]	48	50	120	130
	ESS40001 (CLASS) [2]	96	50	65	73
	LAKE[12]	48	50	41	46
3TC+ABC+LPV	EPZ104057 (HEAT)[52]	96	50	205	242
	ESS100732 (KLEAN)[15]	48	50	288	351
	LAKE[12]	48	50	37	41
3TC+ABC+TDF	ESS30009[17]	NA	NA		
3TC+AZT	AVANTI 2[56]	52	500	9	39
3TC+AZT+EFV	A4001026	NA	NA		
	ACTG 384[47]	28	200	94	114
	ACTG 5095[21]	-	200	NA	NA
	A5175 (PEARLS) [5]	-	1000	NA	NA
	Advanced HIV Mexico[51]	48	50	67	80
	Advanz[25]	144	50	17	31
	AI424-034	NA	NA		
	Chelsea Westminster [35]	48	50	40	40
	CNA30024[10]	48	50	221	253
	DMP 266-006[55]	48	50	93	103
	EPV20001[11]	48	50	333	374
	GESIDA 3093 [3]	48	50	115	133
	GS-01-934[44]	96	50	140	157
	ONCE[30]	NA	NA		
	QUAD[39]	48	50	23	23
	SA Wrkplace HIV Prgm [24]	NA	NA		
	VACH [8]	NA	NA		

Treatment	Study Name	Weeks	VL limit	Successes	Total
3TC+AZT+IDV	Advanz[25]	144	50	8	19
	AVANTI 2[56]	52	500	31	40
	BMS-001[53]	?	50	48	66
	BMS-002[14]	48	50	36	53
	CNAAB3005[54]	48	50	121	151
	CNAB3014[60]	48	50	82	101
	DMP 266-006[55]	48	50	63	80
	OZCOMBO 1[6]	52	50	23	25
3TC+AZT+LPV	CTN 177[22]	NA	NA		
	LORAN [57]	48	50	29	29
3TC+AZT+NFV	ACTG 384 [47]	28	200	61	127
	AI454-148	48	50	119	245
	AI454-152 [20]	NA	NA		
	CNAF3007 [33]	NA	NA		
	COMBINE [41]	NA	NA		
	ESS40002 [26]	96	50	34	57
	ONCE [30]	NA	NA		
3TC+AZT+NVP	COMBINE [41]	NA	NA		
	CTN 177[22]	NA	NA		
	RA (DART substudy) [36]	48	50	207	285
	NVP China[29]	52	50	44	44
	OZCOMBO 2[16]	NA	NA		
3TC+D4T	EARTH 2[19]	52	200	13	31
3TC+D4T+EFV	2NN[59]	48	50	280	343
	ABCDE [42]	96	50	58	64
	AI455-096	NA	NA		
	AI455-099	NA	NA		
	GS-99-903 [18]	144	50	188	209
	N2R[31]	48	50	52	64
3TC+D4T+IDV	BMS-001[53]	?	50	74	87
	EARTH 2[19]	52	200	27	29
	OZCOMBO 1[6]	52	50	20	28
	Thai Indinavir [34]	96	50	55	66
3TC+D4T+LPV	M97-720	NA	NA		
	M98-863[61]	48	50	219	288
	M99-056[13]	48	50	29	34
3TC+D4T+NFV	AI424-008 [37]	48	50	31	83
	ESS40002 [26]	96	50	27	51
	M98-863[61]	48	50	170	277
3TC+D4T+NVP	2NN [59]	48	50	407	529
	N2R [31]	48	50	51	61
	Nigerian ARV Program[23]	NA	NA		
	NVP China[29]	52	50	47	53
	OZCOMBO 2[16]	NA	NA		

Treatment	Study Name	Weeks	VL limit	Successes	Total
3TC+DDI+EFV	GESIDA 3093 [3]	48	50	129	154
	VACH [8]	NA	NA		
3TC+DDI+NVP	ARES [1]	48	50	11	22
3TC+EFV+TDF	ACH443-015	NA	NA		
	GS-99-903 [18]	144	50	203	228
	MK0518-004[32]	48	50	33	35
ATV +FTC+RTV+TDF	ACTG A5202[9]	138	200	263	326
AZT	Delta [4]	48	500	3	66
AZT+3TC	EARTH 2[19]	52	200	8	24
AZT+DDC	Delta [4]	48	500	7	54
AZT+DDI	Delta [4]	48	500	8	53
D4T+DDI	Raffi [46]	24	50	8	59
D4T+DDI+EFV	ACTG 384[47]	28	200	60	109
	FTC301A [48]	48	50	168	224
D4T+DDI+EFV	SENC[38]	NA	NA		
D4T+DDI+NFV	ACTG 384 [47]	28	200	49	107
	AI424-007[49]	48	50	32	84
	AI454-148	48	50	171	489
	AI454-152[20]	NA	NA		
	ARES [1]	48	50	11	26
D4T+DDI+NVP	SENC [38]	NA	NA		
DDI+EFV+FTC	FTC301A [48]	48	50	181	242
EFV+FTC+TDF	A5271015 [40]	NA	NA		
	A5175 (PEARLS) [5]	NA	NA		
	ACTG A5202[9]	138	200	262	350
	Altair [45]	48	50	82	88
	ANRS 129 (BKVIR)	NA	NA		
	CCTG589 [58]	48	50	23	25
	CNA109586 (ASSERT)[43]	48	50	137	151
	GS-01-934[44]	96	50	155	177
	GS-US-236-0102[50]	48	50	288	311
	GS-US-236-0104 [7]	48	50	19	20
	GS-US-264-0110	48	50	317	361
	MK0518-021[28]	NA	NA		
FTC+LPV+TDF	EPZ104057 (HEAT)[52]	96	50	200	228
FTC+TDF+RPV	GS-US-264-0110	48	50	337	384

3 Table 3: Treatment Efficacy Table (Summary)

Below is a chart summarizing, for each treatment, the clinical efficacy determined across all studies. These numbers are the sum of entries in blue and yellow in the chart above.

Treatment	**Successes**	**Total**	**Proportion of patients with VL < 50* ml after 48 weeks**
AZT	3	66	0.05
AZT+DDC	7	54	0.13
AZT+DDI	8	53	0.15
3TC+AZT	9	39	0.23
D4T+DDI+NFV	214	599	0.36
3TC+D4T	13	31	0.42
3TC+AZT+NFV	119	245	0.49
3TC+D4T+NFV	201	360	0.56
3TC+ABC+AZT	466	685	0.69
3TC+D4T+IDV	20	28	0.71
D4T+DDI+EFV	168	224	0.75
3TC+AZT+NVP	251	329	0.76
3TC+D4T+LPV/r	248	322	0.77
3TC+D4T+NVP	505	643	0.79
3TC+AZT+IDV	325	410	0.79
3TC+D4T+EFV	332	407	0.82
3TC+ABC+EFV	502	574	0.87
3TC+AZT+EFV	892	1006	0.89
EFV+FTC+TDF	866	956	0.91
3TC+EFV+TDF	33	35	0.94
3TC+AZT+LPV/r	29	29	1

References

[1] , S. H. Lowe, A. M. J. Wensing, E. A. M. Hassink, R. W. ten Kate, C. Richter, G. Schreij, P. P. Koopmans, J. R. Juttmann, I. van der Tweel, J. M. A. Lange, and J. C. C. Borleffs. Comparison of two once-daily regimens with a regimen consisting of nelfinavir, didanosine, and stavudine in antiretroviral therapy-naïve adults: 48-week results from the antiretroviral regimen evaluation study (ares). *HIV Clinical Trials*, 6(5):235–245, 09 2005.

[2] John A Bartlett, Judy Johnson, Gisela Herrera, Nestor Sosa, Alan Rodriguez, Qiming Liao, Sandy Griffith, David Irlbeck, and Mark S Shaefer. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. *J Acquir Immune Defic Syndr*, 43(3):284–292, Nov 2006.

[3] Juan Berenguer, Juan Gonzalez, Esteban Ribera, Pere Domingo, Jesus Santos, Pilar Miralles, M Angels Ribas, Victor Asensi, Juan Luis Gimeno, Jose Antonio Perez-Molina, Jose Alberto Terron, Juan Miguel Santamaria, and Enric Pedrol. Didanosine, lamivudine, and efavirenz versus zidovudine, lamivudine, and efavirenz for the initial treatment of hiv type 1 infection: final analysis (48 weeks) of a prospective, randomized, noninferiority clinical trial, gesida 3903. *Clin Infect Dis*, 47(8):1083–1092, Oct 2008.

[4] Francoise Brun-Vezinet, Charles Boucher, Clive Loveday, Diane Descamps, Veronique Fauveau, Jacques Izopet, Don Jeffries, Steve Kaye, Corinne Krzyanowski, Andrew Nunn, Rob Schuurman, Jean-Marie Seigneurin, Catherine Tamalet, Richard Tedder, Jonathan Weber, and Gerrit-Jan Weverling. Hiv-1 viral load, phenotype, and resistance in a subset of drug-naive participants from the delta trial. *The Lancet*, 350(9083):983–990, 2015/03/17.

[5] Thomas B. Campbell, Laura M. Smeaton, N. Kumarasamy, Timothy Flanigan, Karin L. Klingman, Cynthia Firnhaber, Beatriz Grinsztejn, Mina C. Hosseinipour, Johnstone Kumwenda, Umesh Lalloo, Cynthia Riviere, Jorge Sanchez, Marineide Melo, Khuanchai Supparatpinyo, Srikanth Tripathy, Ana I. Martinez, Apsara Nair, Ann Walawander, Laura Moran, Yun Chen, Wendy Snowden, James F. Rooney, Jonathan Uy, Robert T. Schooley, Victor De Gruttola, James Gita Hakim, and PEARLS study team of the ACTG. Efficacy and safety of three antiretroviral regimens for initial treatment of hiv-1: A randomized clinical trial in diverse multinational settings. *PLoS Med*, 9(8):e1001290 EP –, 08 2012.

[6] A Carr, J Chuah, J Hudson, M French, J Hoy, M Law, D Sayer, S Emery, and D A Cooper. A randomised, open-label comparison of three highly active antiretroviral therapy regimens including two nucleoside analogues and indinavir for previously untreated hiv-1 infection: the ozcombo1 study. *AIDS*, 14(9):1171–1180, Jun 2000.

[7] Calvin Cohen, Richard Elion, Peter Ruane, David Shamblaw, Edwin DeJesus, Bruce Rashbaum, Steven L Chuck, Kitty Yale, Hui C Liu, David R Warren, Srinivasan Ramanathan, and Brian P Kearney. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of hiv infection. *AIDS*, 25(6):F7–12, Mar 2011.

[8] Manuel Crespo, Esteban Ribera, Ignacio Suarez-Lozano, Pere Domingo, Enric Pedrol, Jose Lopez-Aldeguer, Agustin Munoz, Consuelo Vilades, Trinitario Sanchez, Pompeyo Viciana, Ramon Teira, Maria Luisa Garcia-Alcalde, Antonio Vergara, Fernando Lozano, Maria Jose Galindo, Jaime Cosin, Bernardino Roca, Alberto Terron, Paloma Geijo, Francesc Vidal, and Myriam Garrido. Effectiveness and safety of didanosine, lamivudine and efavirenz versus zidovudine, lamivudine and efavirenz for the initial treatment of hiv-infected patients from the spanish vach cohort. *J Antimicrob Chemother*, 63(1):189–196, Jan 2009.

[9] Eric S. Daar, Camlin Tierney, Margaret A. Fischl, Paul E. Sax, Katie Mollan, Chakra Budhathoki, Catherine Godfrey, Nasreen C. Jahed, Laurie Myers, David Katzenstein, Awny Farajallah, James F. Rooney, Keith A. Pappa, William C.

Woodward, Kristine Patterson, Hector Bolivar, Constance A. Benson, Ann C. Collier, and . Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of hiv-1a randomized trial. *Annals of Internal Medicine*, 154(7):445–456, 04 2011.

[10] Edwin DeJesus, Gisela Herrera, Eugenio Teofilo, Jan Gerstoft, Carlos Beltran Buendia, J David Brand, Cynthia H Brothers, Jaime Hernandez, Steve A Castillo, Tab Bonny, E Randall Lanier, and Trevor R Scott. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive hiv-infected adults. *Clin Infect Dis*, 39(7):1038–1046, Oct 2004.

[11] Edwin DeJesus, Debra McCarty, Charles F Farthing, Denise D Shortino, Beatriz Grinsztejn, Deborah A Thomas, Shannon R Schrader, Steve A Castillo, Michael G Sension, Kevin Gough, and Sam J Madison. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naive adults with hiv infection: a randomized equivalence trial. *Clin Infect Dis*, 39(3):411–418, Aug 2004.

[12] P Echeverria, E Negredo, G Carosi, J Galvez, J L Gomez, A Ocampo, J Portilla, A Prieto, J C Lopez, R Rubio, A Marino, E Pedrol, C Vilades, A del Arco, A Moreno, I Bravo, R Lopez-Blazquez, N Perez-Alvarez, and B Clotet. Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ritonavir, administered with abacavir/lamivudine (kivexa), in antiretroviral-naive patients: a 48-week, multicentre, randomized study (lake study). *Antiviral Res*, 85(2):403–408, Feb 2010.

[13] Joseph J Eron, Judith Feinberg, Harold A Kessler, Harold W Horowitz, Mallory D Witt, Felix F Carpio, David A Wheeler, Peter Ruane, Donna Mildvan, Bienvenido G Yangco, Richard Bertz, Barry Bernstein, Martin S King, and Eugene Sun. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naive hiv-positive patients: a 48-week randomized clinical trial. *J Infect Dis*, 189(2):265–272, Jan 2004.

[14] Joseph J. Jr. Eron, Robert L. Murphy, Dolores Peterson, John Pottage, David M. Parenti, Joseph Jemsek, Susan Swindells, Gladys Sepulveda, Nicholaos Bellos, Bruce C. Rashbaum, Jim Esinhart, Nancy Schoellkopf, Robert Grosso, Michael Stevens, and for the START II Study Team. A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of hiv-1 infected individuals: Selection of thymidine analog regimen therapy (start ii)*. *AIDS*, 14(11), 2000.

[15] Joseph Jr Eron, Patrick Yeni, Joseph Jr Gathe, Vicente Estrada, Edwin DeJesus, Schlomo Staszewski, Philip Lackey, Christine Katlama, Benjamin Young, Linda Yau, Denise Sutherland-Phillips, Paul Wannamaker, Cindy Vavro, Lisa Patel, Jane Yeo, and Mark Shaefer. The klean study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of hiv infection over 48 weeks: a randomised non-inferiority trial. *Lancet*, 368(9534):476–482, Aug 2006.

[16] Martyn French, Janaki Amin, Norman Roth, Andrew Carr, Matthew Law, Sean Emery, Fraser Drummond, and David Cooper. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated hiv-1 infection: the ozcombo 2 study. *HIV Clin Trials*, 3(3):177–185, May-Jun 2002.

[17] Joel E Gallant, Allan E Rodriguez, Winkler G Weinberg, Benjamin Young, Daniel S Berger, Michael L Lim, Qiming Liao, Lisa Ross, Judy Johnson, and Mark S Shaefer. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in hiv-infected antiretroviral-naive subjects. *J Infect Dis*, 192(11):1921–1930, Dec 2005.

[18] Joel E Gallant, Schlomo Staszewski, Anton L Pozniak, Edwin DeJesus, Jamal M A H Suleiman, Michael D Miller, Dion F Coakley, Biao Lu, John J Toole, and Andrew K Cheng. Efficacy and safety of tenofovir df vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*, 292(2):191–201, Jul 2004.

[19] F Garcia, M M Alonso, J Romeu, H Knobel, J Arrizabalaga, E Ferrer, D Dalmau, I Ruiz, F Vidal, A Frances, F Segura, J L Gomez-Sirvent, A Cruceta, B Clotet, T Pumarola, T Gallart, W A O'Brien, J M Miro, and J M Gatell. Comparison of immunologic restoration and virologic response in plasma, tonsillar tissue, and cerebrospinal fluid in hiv-1-infected patients treated with double versus triple antiretroviral therapy in very early stages: The spanish earth-2 study. early anti-retroviral therapy study. *J Acquir Immune Defic Syndr*, 25(1):26–35, Sep 2000.

[20] Joseph Jr. Gathe, Roberto Badaro, Ashraf Grimwood, Lori Abrams, Ken Klesczewski, Anne Cross, and Colin McLaren. Antiviral activity of enteric-coated didanosine, stavudine, and nelfinavir versus zidovudine plus lamivudine and nelfinavir. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 31(4), 2002.

[21] Roy M. Gulick, Heather J. Ribaudo, Cecilia M. Shikuma, Stephanie Lustgarten, Kathleen E. Squires, William A. Meyer, Edward P. Acosta, Bruce R. Schackman, Christopher D. Pilcher, Robert L. Murphy, William E. Maher, Mallory D. Witt, Richard C. Reichman, Sally Snyder, Karin L. Klingman, and Daniel R. Kuritzkes. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of hiv-1 infection. *New England Journal of Medicine*, 350(18):1850–1861, 2014/08/08 2004.

[22] Marianne Harris, Hélène Côté, Claudia Ochoa, Clotilde Allavena, Eugenia Negredo, Anona Thorne, Pedro Cahn, Carlos Zala, Francois Raffi, Bonaventura Clotet, Joel Singer, Julio Montaner, and The CTN 177 Study Team. A randomized, open-label study of a nucleoside analogue reverse transcriptase inhibitor-sparing regimen in antiretroviral-naive hiv-infected patients. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 50(3), 2009.

[23] Emmanuel O Idigbe, Taiwo A Adewole, Geoffrey Eisen, Phyllis Kanki, Nkiru N Odunukwe, Dan I Onwujekwe, Rosemary A Audu, Idowu D Araoyinbo, Joseph I Onyewuche, Oluwamuyiwa B Salu, John A Adedoyin, and Adesola Z Musa. Management of hiv-1 infection with a combination of nevirapine, stavudine, and lamivudine: a preliminary report on the nigerian antiretroviral program. *J Acquir Immune Defic Syndr*, 40(1):65–69, Sep 2005.

[24] Senoge S Seatlanyane P et al. Innes C CS, Maraisane M. 24 and 36 month outcomes among hiv-infected individuals starting antiretroviral therapy in a workplace program in south africa. In Abstract no MOPE0046, editor, *AIDS 2008 - XVII International AIDS Conference*, 2008.

[25] Judith Pich Pere Domingo Elena Ferrer José R. Arribas Esteban Ribera Julio Arrizabalaga Montserrat Loncá Anna Cruceta Elisa de Lazzari Montserrat Fuster Daniel Podzamczer Montserrat Plana José M. Miró, Christian Manzardo and José M. Gatell. Immune reconstitution in severely immunosuppressed antiretroviral-naive hiv type 1-infected patients using a nonnucleoside reverse transcriptase inhibitor-based or a boosted protease inhibitor-based antiretroviral regimen: Three-year results (the advanz trial): A randomized, controlled trial. *AIDS Research and Human Retroviruses*, 26(7):747–757, July 2010.

[26] P N Kumar, A Rodriguez-French, M A Thompson, K T Tashima, D Averitt, P G Wannamaker, V C Williams, M S Shaefer, G E Pakes, and K A Pappa. A prospective, 96-week study of the impact of trizivir, combivir/nelfinavir, and lamivudine/stavudine/nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naive patients: effect of sex and ethnicity. *HIV Med*, 7(2):85–98, Mar 2006.

[27] Princy N Kumar, Patricia Salvato, Anthony Lamarca, Edwin Dejesus, Parul Patel, Daniel McClernon, Allison Florance, and Mark S Shaefer. A randomized, controlled trial of initial anti-retroviral therapy with abacavir/lamivudine/zidovudine twice-daily compared to atazanavir once-daily with lamivudine/zidovudine twice-daily in hiv-infected patients over 48 weeks (ess100327, the action study). *AIDS Res Ther*, 6:3, 2009.

[28] Jeffrey L Lennox, Edwin DeJesus, Adriano Lazzarin, Richard B Pollard, Jose Valdez Ramalho Madruga, Daniel S Berger, Jing Zhao, Xia Xu, Angela Williams-Diaz, Anthony J Rodgers, Richard J O Barnard, Michael D Miller, Mark J DiNubile, Bach-Yen Nguyen, Randi Leavitt, and Peter Sklar. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with hiv-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*, 374(9692):796–806, Sep 2009.

[29] Taisheng Li, Yi Dai, Jiqiu Kuang, Jingmei Jiang, Yang Han, Zhifeng Qiu, Jing Xie, Lingyan Zuo, and Yanling Li. Three generic nevirapine-based antiretroviral treatments in chinese hiv/aids patients: Multicentric observation cohort. *PLoS ONE*, 3(12):e3918 EP –, 12 2008.

[30] Franco Maggiolo, Diego Ripamonti, Gianpietro Gregis, Gianpaolo Quinzan, Annapaola Callegaro, Claudio Arici, Laura Ravasio, and Fredy Suter. Once-a-day therapy for hiv infection: a controlled, randomized study in antiretroviral-naive hiv-1-infected patients. *Antivir Ther*, 8(4):339–346, Aug 2003.

[31] Weerawat Manosuthi, Somnuek Sungkanuparph, Preecha Tantanathip, Aroon Lueangniyomkul, Wiroj Mankatitham, Wisit Prasithsirskul, Sunantha Burapatarawong, Supeda Thongyen, Sirirat Likanonsakul, Unchana Thawornwa, Vilai-

wan Prommool, and Kiat Ruxrungtham. A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in hiv-infected patients receiving rifampicin: the n2r study. *Clin Infect Dis*, 48(12):1752–1759, Jun 2009.

[32] Martin Markowitz, Bach-Yen Nguyen, Eduardo Gotuzzo, Fernando Mendo, Winai Ratanasuwan, Colin Kovacs, Guillermo Prada, Javier O Morales-Ramirez, Clyde S Crumpacker, Robin D Isaacs, Lucinda R Gilde, Hong Wan, Michael D Miller, Larissa A Wenning, and Hedy Teppler. Rapid and durable antiretroviral effect of the hiv-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with hiv-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr*, 46(2):125–133, Oct 2007.

[33] Sophie Matheron, Diane Descamps, Francois Boue, Jean-Michel Livrozet, Alain Lafeuillade, Christian Aquilina, Didier Troisvallets, Agnes Goetschel, Francoise Brun-Vezinet, Jean-Philippe Mamet, and Cecile Thiaux. Triple nucleoside combination zidovudine/lamivudine/abacavir versus zidovudine/lamivudine/nelfinavir as first-line therapy in hiv-1-infected adults: a randomized trial. *Antivir Ther*, 8(2):163–171, Apr 2003.

[34] Piroon Mootsikapun, Ploenchan Chetchotisakd, Siriluck Anunnatsiri, and Parichat Boonyaprawit. Efficacy and safety of indinavir/ritonavir 400/100 mg twice daily plus two nucleoside analogues in treatment-naive hiv-1-infected patients with cd4+ t-cell counts <200 cells/mm3: 96-week outcomes. *Antivir Ther*, 10(8):911–916, 2005.

[35] Graeme Moyle, Christopher Higgs, Alastair Teague, Sundhiya Mandalia, Mark Nelson, Margaret Johnson, Martin Fisher, and Brian Gazzard. An open-label, randomized comparative pilot study of a single-class quadruple therapy regimen versus a 2-class triple therapy regimen for individuals initiating antiretroviral therapy. *Antivir Ther*, 11(1):73–78, 2006.

[36] P Munderi, A S Walker, C Kityo, A G Babiker, F Ssali, A Reid, J H Darbyshire, H Grosskurth, P Mugyenyi, D M Gibb, and C F Gilks. Nevirapine/zidovudine/lamivudine has superior immunological and virological responses not reflected in clinical outcomes in a 48-week randomized comparison with abacavir/zidovudine/lamivudine in hiv-infected ugandan adults with low cd4 cell counts. *HIV Med*, 11(5):334–344, May 2010.

[37] Robert L Murphy, Ian Sanne, Pedro Cahn, Praphan Phanuphak, Lisa Percival, Thomas Kelleher, and Michael Giordano. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS*, 17(18), 2003.

[38] Marina Nunez, Vincent Soriano, Luz Martin-Carbonero, Ana Barrios, Pablo Barreiro, Francisco Blanco, Teresa Garcia-Benayas, and Juan Gonzalez-Lahoz. Senc (spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in hiv-infected naive individuals. *HIV Clin Trials*, 3(3):186–194, May-Jun 2002.

[39] Chloe Orkin, Justin Stebbing, Mark Nelson, Mark Bower, Margaret Johnson, Sundhiya Mandalia, Rachael Jones, Graeme Moyle, Martin Fisher, and Brian Gazzard. A randomized study comparing a three- and four-drug haart regimen in first-line therapy (quad study). *J Antimicrob Chemother*, 55(2):246–251, Feb 2005.

[40] A. Pozniak E. Weil P. Pulik D. Cooper R. Kaplan A. Lazzarin H. Valdez Goodrich C. Craig J. Mori M. Tawadrous P. Vernazza, C. Wang. Efficacy and safety of lersivirine (uk-453,061) vs. efavirenz in antiretroviral treatment-naïve hiv-1-infected patients: week 48 primary analysis results from an ongoing, multicentre, randomised, double-blind, phase iib trial (study a5271015). In *6th IAS conference on HIV Pathogenesis, Treatment and Preventation*, 2011.

[41] Daniel Podzamczer, Elena Ferrer, Ezequiel Consiglio, Jose Maria Gatell, Pepa Perez, Jose Luis Perez, Elena Luna, Alicia Gonzalez, Enric Pedrol, Luisa Lozano, Imma Ocana, Josep Maria Llibre, Arnaldo Casiro, Miquel Aranda, Pilar Barrufet, Javier Martinez-Lacasa, Jose Maria Miro, Xavier Badia, Alfonso Casado, Sergio Lupo, Pedro Cahn, Manel Manos, and Jordi Estela. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in hiv-infected naive patients (the combine study). *Antivir Ther*, 7(2):81–90, Jun 2002.

[42] Daniel Podzamczer, Elena Ferrer, Pochita Sanchez, JoséM Gatell, Manel Crespo, Cesar Fisac, Montse Lonca, Jose Sanz, Jordi Niubo, Sergio Veloso, Josep M Llibre, Pilar Barrufet, María A Ribas, Esperanza Merino, Esteban Ribera, Javier Martínez-Lacasa, Carlos Alonso, Miquel Aranda, Federico Pulido, Juan Berenguer, Antonio Delegido, Juan D Pedreira, Ana Lérida, Rafael Rubio, Luis del Río, and for the ABCDE (Abacavir vs. d4T (stavudine) plus efavirenz) Study Team. Less lipoatrophy and better lipid profile with abacavir as compared to stavudine: 96-week results of a randomized study. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 44(2), 2007.

[43] Frank A Post, Graeme J Moyle, Hans Jurgen Stellbrink, Pere Domingo, Daniel Podzamczer, Martin Fisher, Anthony G Norden, Matthias Cavassini, Armin Rieger, Marie-Aude Khuong-Josses, Teresa Branco, Helen C Pearce, Naomi Givens, Cindy Vavro, and Michael L Lim. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, hiv-1-infected adults: 48-week results from the assert study. *J Acquir Immune Defic Syndr*, 55(1):49–57, Sep 2010.

[44] Anton L Pozniak, Joel E Gallant, Edwin DeJesus, Jose R Arribas, Brian Gazzard, Rafael E Campo, Shan-Shan Chen, Damian McColl, Jeffrey Enejosa, John J Toole, and Andrew K Cheng. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes–a 96-week analysis. *J Acquir Immune Defic Syndr*, 43(5):535–540, Dec 2006.

[45] Rebekah L. Puls, Preeyaporn Srasuebkul, Kathy Petoumenos, Christoph Boesecke, Chris Duncombe, Waldo H. Belloso, Jean-Michel Molina, Lin Li, Anchalee Avihingsanon, Brian Gazzard, David A. Cooper, Sean Emery, and Altair Study Group. Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, hiv-infected subjects: Week 48 data from the altair study. *Clinical Infectious Diseases*, 51(7):855–864, 10 2010.

[46] François Raffi, Véronique Reliquet, Sylvie Auger, Jean-Marc Besnier, Jean-Marie Chennebault, Eric Billaud, Christian Michelet, Philippe Perre, Alain Lafeuillade, Thierry May, and Sylviane Billaudel. Efficacy and safety of stavudine and didanosine combination therapy in antiretroviral experienced patients. *AIDS*, 12(15), 1998.

[47] Gregory K. Robbins, Victor De Gruttola, Robert W. Shafer, Laura M. Smeaton, Sally W. Snyder, Carla Pettinelli, Michael P. Dubé, Margaret A. Fischl, Richard B. Pollard, Robert Delapenha, Linda Gedeon, Charles van der Horst, Robert L. Murphy, Mark I. Becker, Richard T. D'Aquila, Stefano Vella, Thomas C. Merigan, and Martin S. Hirsch. Comparison of sequential three-drug regimens as initial therapy for hiv-1 infection. *New England Journal of Medicine*, 349(24):2293–2303, 2014/08/07 2003.

[48] Michael S Saag, Pedro Cahn, Francois Raffi, Marcelo Wolff, Daniel Pearce, Jean-Michel Molina, William Powderly, Audrey L Shaw, Elsa Mondou, John Hinkle, Katyna Borroto-Esoda, Joseph B Quinn, David W Barry, and Franck Rousseau. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA*, 292(2):180–189, Jul 2004.

[49] Ian Sanne, Peter Piliero, Kathleen Squires, Alexandra Thiry, Steven Schnittman, and AI424-007 Clinical Trial Group. Results of a phase 2 clinical trial at 48 weeks (ai424-007): A dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 32(1), 2003.

[50] Paul E Sax, Edwin DeJesus, Anthony Mills, Andrew Zolopa, Calvin Cohen, David Wohl, Joel E Gallant, Hui C Liu, Lijie Zhong, Kitty Yale, Kirsten White, Brian P Kearney, Javier Szwarcberg, Erin Quirk, and Andrew K Cheng. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of hiv-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*, 379(9835):2439–2448, Jun 2012.

[51] Juan Sierra-Madero, Angelina Villasis-Keever, Patricia Méndez, Juan Luis Mosqueda-Gómez, Indiana Torres-Escobar, Fernanda Gutiérrez-Escolano, Irene Juárez-Kasusky, Martín Magana-Aquino, Carmen Ramos-Santos, Leticia Pérez-Saleme, Sigfrido Rangel-Frausto, Barbara Antuna-Puente, Luis Enrique Soto-Ramírez, Vivian Lima, Franciso Belaunzarán-Zamudio, Brenda Crabtree-Ramírez, and Julio Montaner. Prospective, randomized, open label trial of efavirenz vs lopinavir/ritonavir in hiv+ treatment-naive subjects with cd4+<200 cell/mm3 in mexico. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 53(5), 2010.

[52] Kimberly Y Smith, Parul Patel, Derek Fine, Nicholaos Bellos, Louis Sloan, Philip Lackey, Princy N Kumar, Denise H Sutherland-Phillips, Cindy Vavro, Linda Yau, Paul Wannamaker, and Mark S Shaefer. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial hiv treatment. *AIDS*, 23(12):1547–1556, Jul 2009.

[53] Kathleen E. Squires, Roy Gulick, Pablo Tebas, Jorge Santana, Victor Mulanovich, Rebecca Clark, Bienvenido Yangco, Steven I. Marlowe, David Wright, Calvin Cohen, Timothy Cooley, Joseph Mauney, Katharina Uffelman, Nancy Schoellkopf, Robert Grosso, and Michael Stevens. A comparison of stavudine plus lamivudine versus zidovudine plus lamivudine in combination with indinavir in antiretroviral naive individuals with hiv infection: selection of thymidine analog regimen therapy (start i). *AIDS*, 14(11), 2000.

[54] S Staszewski, P Keiser, J Montaner, F Raffi, J Gathe, V Brotas, C Hicks, S M Hammer, D Cooper, M Johnson, S Tortell, A Cutrell, D Thorborn, R Isaacs, S Hetherington, H Steel, and W Spreen. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive hiv-infected adults: A randomized equivalence trial. *JAMA*, 285(9):1155–1163, Mar 2001.

[55] S Staszewski, J Morales-Ramirez, K T Tashima, A Rachlis, D Skiest, J Stanford, R Stryker, P Johnson, D F Labriola, D Farina, D J Manion, and N M Ruiz. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of hiv-1 infection in adults. study 006 team. *N Engl J Med*, 341(25):1865–1873, Dec 1999.

[56] The AVANTI study group. Avanti 2. randomized, double-blind trial to evaluate the efficacy and safety of zidovudine plus lamivudine versus zidovudine plus lamivudine plus indinavir in hiv-infected antiretroviral-naive patients. *AIDS*, 14(4), 2000.

[57] K. U. Ulbricht, G. M. Behrens, M. Stoll, B. Salzberger, H. Jessen, A. B. Jessen, B. Kuhlmann, H. Heiken, A. Trein, and R. E. Schmidt. A multicenter, open labeled, randomized, phase iii study comparing lopinavir/ritonavir plus atazanavir to lopinavir/ritonavir plus zidovudine and lamivudine in naive hiv-1-infected patients: 48-week analysis of the loran trial.

[58] S. Jain M. Goicoechea M. Dube S. Kerkar S. Schneider C. Kemper C. Diamond S. Sun A. Hermes K. Bailey E. Daar R. Haubrich California Collaborative Treatment Group V. Bowman, G. Rieg. 48 week results of a pilot randomized study of an nucleoside reverse transcriptase inhibitor (nrti)-sparing regimen of raltegravir (ral) + lopinavir/ritonavir (lpv/r) versus efavirenz/tenofovir disoproxil fumarate /emtricitabine (efv/tdf/ftc) in antiretro. In *6th IAS conference on HIV Pathogenesis, Treatment and Preventation*, 2011.

[59] F van Leth, P Phanuphak, K Ruxrungtham, E Baraldi, S Miller, B Gazzard, P Cahn, UG Lalloo, IP van der Westhuizen, DR Malan, MA Johnson, BR Santos, F Mulcahy, R Wood, GC Levi, G Reboredo, K Squires, I Cassetti, D Petit, F Raffi, C Katlama, RL Murphy, A Horban, JP Dam, E Hassink, R van Leeuwen, P Robinson, FW Wit, and JMA Lange. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2nn study. *The Lancet*, 363(9417):1253–1263, 4 2004.

[60] Asda Vibhagool, Pedro Cahn, Mauro Schechter, Fiona Smaill, Luis Soto-Ramirez, Giampiero Carosi, Maria Montroni, Cristina E Pharo, Jamie C Jordan, Nicola E Thomas, and Gill Pearce. Triple nucleoside treatment with abacavir plus

the lamivudine/zidovudine combination tablet (com) compared to indinavir/com in antiretroviral therapy-naive adults: results of a 48-week open-label, equivalence trial (cna3014). *Curr Med Res Opin*, 20(7):1103–1114, Jul 2004.

[61] Sharon Walmsley, Barry Bernstein, Martin King, Jose Arribas, Gildon Beall, Peter Ruane, Margaret Johnson, David Johnson, Richard Lalonde, Anthony Japour, Scott Brun, and Eugene Sun. Lopinavir-ritonavir versus nelfinavir for the initial treatment of hiv infection. *N Engl J Med*, 346(26):2039–2046, Jun 2002.