IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX CORP.
Petitioner

v.

VIIV HEALTHCARE CO. and
VIIV HEALTHCARE UK LTD.
Patent Owner

Case IPR2014-00876
Patent 6,417,191 B1

APOTEX CORP.'S REPLY TO PATENT OWNERS' RESPONSE TO THE PETITION

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

I. ViiV has not rebutted Apotex's showing of obviousness.

ViiV has failed to rebut Apotex's showing that the ’191 patent claims would have been obvious over Cameron (APO1002) and Daluge (APO1003).

A. A POSA would have had a reason to combine abacavir with AZT/3TC.

ViiV and Apotex agree that a POSA would have been motivated to improve upon the most effective treatment in the prior art – the AZT/3TC combination.[1] POR at 12, 18-19, 44; APO1071, 16:6-23; ViiV2009, ¶67; Pet. at 2, 14. But in contrast to ViiV's argument that there was a "vast universe" of compounds to choose from, Dr. Ho admitted that the combination of AZT/3TC was "a breakthrough" and "a better combination than other combinations . . . So we wanted to come up with new therapies *that would build on that*." APO1071, 33:1-2, 16:17-23 (emphasis added). Accordingly, a POSA would have started with the most successful combination to date, AZT/3TC, and added a third drug to achieve a better HIV therapy. *Id.* APO1050, 45:2:2; APO1067, ¶¶15-30.

1. Multidrug combinations were recognized as the future of HIV treatment.

ViiV portrayed combination therapy for HIV as uncertain, but even before the results of the successful AZT/3TC trials were public, a POSA would have appreciated that "drugs should be given *simultaneously for optimal benefit*." APO1004, Abstract (emphasis added). As Victoria Johnson summed up on the eve

[1] The challenged claims do not *require* an improvement over the art. *See* § IB.

of the AZT/3TC trial results, "[u]ltimately, we need better drugs, *in combination*, which significantly impact on HIV-1 burden to achieve a more complete viral suppression and to reduce selection of drug resistant viral variants." APO1004, Abstract (emphasis added). The breakthrough AZT/3TC trial results only provided confirmation that combination therapies were the future of HIV treatment. APO1004; APO1009, 1291; APO1050, 45-46; APO1067, ¶¶18-26, 68-75.

2. Researchers were actively investigating triple-NRTI therapies.

ViiV argues that a POSA would not have combined three NRTIs because of "toxicity concerns" (POR, 23-26), but the facts bely ViiV's argument. In January 1995, Glaxo, Inc., reported an ongoing trial using AZT, 3TC, and ddI—all NRTIs—in pediatric patients. APO1042, 265; APO1067, ¶21, 44, 75. So POSAs were aware that both *preclinical research and clinical trials of triple combinations of NRTIs* were ongoing as of March 30, 1995. APO1042, 265, 268; APO1067, ¶¶18-22, 75. Likewise, St. Clair reported "the most consistent triple-drug combination, demonstrating superior activity ... was AZT + DDI + 3TC. . . ." APO1042, 268; APO1067, ¶ 20. Though ViiV maintains that POSAs did not pursue combinations of three NRTIs before the filing date, even Dr. Ho acknowledged the existence of such triple-NRTI studies when cross-examined. APO1071, 40:22-41:5; APO1067, ¶22. Thus, a POSA would not have been dissuaded from using a triple-NRTI combination. APO1032; APO1042, 265, 268;

APO1067, ¶¶18-22, 72-75. To the contrary, triple-NRTI combinations were an active area of research. APO1067, ¶¶18-22, 72-75. For this reason alone, the Board should give little weight to ViiV's assertion that toxicity concerns dissuaded POSAs from using triple-NRTI combinations. APO1067, ¶¶53-56, 72-75.

Also, before March 1995, newer second-generation NRTIs, including 3TC and abacavir, were known to have much better toxicity profiles relative to first-generation NRTIs. APO1050, 45:2:3; APO1067, ¶¶17, 27-29; APO1003. And a POSA would have understood that "[s]cientists are finally waking up and 'smelling the data.' We are realizing that nucleosides are the only approved antiretroviral drugs and that *they are not all the same…thus destroying the fallacy that there is no 'non-toxic nucleoside' for retroviral therapy*." APO1050, 45:2:3. So although ViiV tries to paint NRTIs with a broad brush, the art taught a POSA that newer NRTIs such as 3TC and abacavir had, at most, very low levels of toxicity. APO1050, 45; APO1003; ViiV2006, I82; APO1067, ¶¶72-75.

3. The properties of a drug were more important than its mechanistic class when considering it for a combination.

ViiV argues that a POSA would have focused on non-NRTI classes of drugs for potential combinations (POR at 14), but the art taught that "[i]t is probably less important which particular targets in the HIV-1 replicative cycle are selected for inhibition by the components of a multiple-drug regimen, but rather that each agent

has proven *potent, independent, and nontoxic antiviral activity in vivo*." APO1004, 908:1:4 (emphasis added); APO1067, ¶¶5, 24. As Dr. Ho admitted, the major features to consider when selecting combination therapy drugs were, "[t]he potency of each compound[,] [t]he pharmacokinetic properties, [and] the side effect profile." APO1071, 28:9-20; APO1067, ¶¶24, 25, 107.

4. A POSA would have chosen abacavir from a limited class of candidate compounds.

Researchers recognized abacavir as an "important candidate for *combination therapy*." APO1003; ViiV2006 I82, I84, I86, I88 (emphasis added); APO1067, ¶¶27-29, 67. In fact, in March 1995, researchers stated that human clinical "trials with [abacavir] are progressing to multiple-dose regimens, *including combinations with Retrovir*® [AZT]" based on very positive preclinical and clinical data showing good potency and low toxicity. ViiV2024, 8; ViiV2006, I82 (emphasis added); APO1067, ¶¶52, 67. As ViiV's expert conceded, "the drugs with the most desirable properties are moved forward to clinical trials." APO1071, 93:14-18. Accordingly, abacavir stood out among the NRTIs as having very desirable properties useful for combination therapy. ViiV2024, 8; ViiV2006, I82; APO1067, ¶¶23-29. And a POSA would have recognized each of abacavir's desirable properties—high potency, low toxicity, synergy with AZT, good bioavailability and pharmacokinetics, resistance profile, and its penetration into the CNS.

APO1003; ViiV1006; APO1006, ¶¶37-38; APO1067, ¶¶27-29, 48-67.

A POSA would not have been swimming blindly in a sea of "hundreds of compounds," as ViiV would have the Board believe. POR at 14-15; APO1067, ¶¶5, 15-29. Of course most of the compounds ViiV alleges were available to combine with AZT/3TC were not in clinical trials as of 1995, or were inappropriate for human testing at their stage of development. APO1067, ¶¶76-83; ViiV2009, ¶¶38-39. ViiV does not show how any of the compounds in clinical trials as of March 1995 had the unique set of properties present in abacavir that would have motivated a POSA to combine it with the successful AZT/3TC combination. POR at 15-16; APO1067, ¶¶27-29, 67, 76-83.

Abacavir was known to be potent. Dr. Ho admitted that potency was one of the "major" factors in selecting drugs for combination therapy. APO1071, 28:9-20; APO1067, ¶¶25, 107. Daluge stated that abacavir "was equivalent in potency to AZT when tested . . . against [multiple] fresh clinical isolates of HIV 1 from AZT-naïve patients." APO1003. ViiV questions abacavir's potency by arguing that Tisdale shows that abacavir was less potent than AZT against a single laboratory HIV strain. ViiV2006, I82 ("Tisdale"); POR at 21; ViiV2009 ¶46. But ViiV ignores Tisdale's demonstration that abacavir's activity was "equivalent to the historical value of AZT" when tested against *8 separate clinical isolates* of HIV. ViiV2006, I82; APO1067, ¶¶49-50. And Tisdale concluded that abacavir is "an

important candidate for further development as an anti-HIV drug *for combination therapy*." *Id*. (emphasis added).

Abacavir also had known synergy with AZT. APO1003; ViiV2006, I82; APO1067, ¶¶59-60. In 1995, the art appreciated that "[c]ertain combinations of anti-HIV agents appear to have synergistic anti-HIV activity *in vitro*, and this may provide *yet another rationale for combination therapy*." ViiV2051, 107:4 (emphasis added); APO1071, 27:22-28:8. The Daluge and Tisdale references teach that abacavir shows synergy with AZT. APO1003; ViiV2006, I82; APO1067, ¶¶27-29, 59-60. Contrary to ViiV's mischaracterizations about the relevance of synergy studies conducted *in vitro* (POR at 30), *in vitro* synergy studies were routinely performed as part of drug-development efforts and considered valuable to predict which drugs work well in combination. APO1067, ¶¶19, 87. For example, as Yarchoan and Broder explained, the *in vitro* activity of NRTIs "can be a fairly good predictor of clinical activity." ViiV2051, 101; *See also e.g.*, APO1003; APO1010; ViiV2006; APO1050, 46:1:4; APO1067, ¶¶53, 59-60.

Abacavir was known to be safe in humans. ViiV paints all NRTIs with the same brush and argues that NRTIs are toxic. POR at 23. But Daluge teaches that abacavir is "safe," with only "mild, reversible" side effects at the highest doses in animals, and has "300-fold" less toxicity than AZT *in vitro*. APO1003; APO1006, ¶39; APO1067, ¶¶53-56. And Ching *et al*. concluded from toxicological studies of

abacavir, concluding that "[t]his favorable preclinical profile makes [abacavir] an attractive candidate for evaluation in HIV-infected patients." ViiV2006; APO1067, ¶56. And dose-escalation studies in humans had shown "encouraging kinetics and tolerance" for patients receiving abacavir. ViiV2024, 8; APO1067, ¶52.

ViiV generically portrays any toxicity as something that would dissuade a POSA from even attempting to use a given therapy. POR at 23-26. But Dr. Ho admitted he considered a side effect such as "a minor rash for a day or two" a toxicity. APO1071, 27:2-4; APO1067, ¶53. And, as Dr. Ho also conceded on cross-examination "[i]f it’s a side effect that physicians deem as insignificant or manageable, [a drug] may still move forward." APO1071, 26:13-19. ViiV's POR does not establish that POSAs would have expected a combination of AZT, 3TC, and abacavir to have *unacceptable* levels of toxicity, and the claims do not require the *absence* of toxicity. APO1067. ¶¶23-29, 72-75.

ViiV also argues that combinations of NRTIs increased toxicities. POR at 24. But in the AZT/3TC trials, "[t]here were no more adverse events in the 3TC/AZT group than in the AZT monotherapy group." APO1013, 2. In fact, 3TC had very little associated toxicity reported in the literature whether alone or in combination with AZT. *Id.*; APO1050, 45:2:3; APO1067, ¶¶17, 72-75. And abacavir’s "encouraging kinetics and tolerance" prompted "progressing to multiple-dose regimens, including *combinations with Retrovir* ® [AZT]."

ViiV2024; 8 (emphasis added); APO1067, ¶67. Notably, ViiV did not point to a single reference expressing concern about toxicity with abacavir. ViiV's failure is not surprising since the art showed just the opposite—patients tolerated abacavir. ViiV2024; 8; ViiV2006; APO1003; APO1006, ¶38; APO1067, ¶¶53-56.

ViiV wrongly argues that a POSA would have been concerned about abacavir's toxicity because abacavir shared the same active metabolite as carbovir, an earlier-generation HIV drug that had unacceptable toxicity. POR at 24. But by March 1995 it was known that in humans, "[a]s in animals, carbovir levels were negligible" after abacavir treatment. ViiV2024, 8; APO1067, ¶55. Further, researchers showed by March 1995 that abacavir did not raise the same toxicity concerns as carbovir, notwithstanding a common metabolite. And as Dr. Ho admitted, phase I trials with abacavir would not have begun had the toxicity concerns not been resolved. APO1060, 26:2:2; APO1067, ¶¶25-29; APO1025, 219:5-9, 222:7-10, 224:8-13. Therefore, ViiV's argument, that a POSA would have had toxicity concerns about abacavir is unavailing in light of the positive clinical and preclinical results showing abacavir's safety. APO1067, ¶¶27-29,

ViiV's arguments ignore that there was no negative human abacavir toxicity reported as of March 1995, even though clinical trials with abacavir had started at least six months earlier. APO1060, 26:2:2; APO1067, ¶¶27-29, 53-56, 72-75. And after phase I trials, abacavir was regarded as safe to progress to combination

regimens with AZT in humans. ViiV2024, 8. Accordingly, a POSA would not have expected abacavir, 3TC, and AZT to have unacceptably high toxicity in combination. APO1067, ¶¶27-29, 53-56, 72-75. ViiV's generalizations about NRTI toxicities simply do not apply to the combination of AZT, 3TC, and abacavir. APO1050; APO1003; ViiV2006; ViiV2024, 8; APO1067, ¶¶72-75.

Abacavir's penetration of the CNS was another positive feature that would have prompted its use. As Dr. Ho admitted on cross-examination, CNS penetration was a factor a POSA would consider in evaluating HIV drugs. APO1071, 45:20-46:15l APO1067, ¶¶57-58. Similarly, the art taught that "[t]he ability of a drug to penetrate the CNS . . . has become increasingly important . . . [and] newly developed antiviral drugs should be able to cross the blood-brain barrier." APO1014, 152:4. Drugs that effectively crossed the blood–brain barrier were thought to be important in eliminating viral reservoirs were known to occur in the CNS. APO1014, 152:4; APO1048, 354:1:4; APO1067, ¶¶57-58. And as Dr. Ho admitted, "not all drugs will penetrate" into the CNS, and it is "a bonus" when they do. APO1071, 46:16-19, 47:7-17. ViiV does not dispute Daluge's teaching that abacavir penetrates the CNS well. APO1003; ViiV2009, ¶50. Thus, abacavir's ability to penetrate the CNS would have weighted in favor of combining it with AZT/3TC. APO1067, ¶¶27-29, 57-58.

Abacavir was known to have good pharmacokinetics. Abacavir's good

oral bioavailability and pharmacokinetic profile, which ViiV does not dispute, would have motivated a POSA to choose abacavir. ViiV2006, I82; APO1067, ¶¶51-52. Dr. Ho admitted "[t]he pharmacokinetic profile of a drug is very important," and was one of the "principal" and "major" factors involved in drug selection. APO1071, 19:8-23, 28:9-20. Thus the extensive analysis of the pharmacokinetics of abacavir in mice, monkeys, and humans and its "excellent" oral bioavailability would have been further reasons for a POSA to combine abacavir with AZT/3TC. APO1003; ViiV2006; ViiV2024, 8; APO1067, ¶¶51-52.

Researchers focused on combinations of drugs targeting different bases. ViiV alleges that all NRTIs are directed to the same target and that a POSA would not have been motivated to use combinations of NRTIs for that reason. POR at 26-27; ViiV1009, ¶46. But ViiV's argument is unfounded; researchers actively pursued combinations of NRTIs, including triple combinations. APO1042, 265; ViiV2024, 8; APO1012; ViiV2059; APO1032; APO1067, ¶¶61-66, 72-75. And the most successful HIV therapy as of March 1995 was a combination two NRTIs: AZT and 3TC. APO1067, ¶17; APO1012. Moreover, clinical trials of combination therapies included AZT/3TC, AZT/ddC, AZT/ddI, AZT/3TC/ddI, and AZT/3TC/ddC. APO1012; APO1042, 265; APO1044, 7:1:5; ViiV2059; APO1072. APO1067, ¶¶7, 20-22, 72-75. That abacavir targets a different base than AZT or 3TC would have been another reason to choose abacavir for a triple-drug

combination. APO1067, ¶¶61-66. ViiV seeks to discount this feature of abacavir and contends that researchers would have also considered combining NRTIs targeting the same nucleotide bases. POR at 29. But ViiV fails to identify any research article or clinical trial testing combinations of NRTI's targeting the *same* base. To the contrary, the art-recognized approach to combination therapy involved using NRTIs that targeted different bases, as shown above. APO1012; ViiV2059; APO1072; APO1067, ¶¶ 19-21, 61-66; APO1042, 265.

Abacavir was recognized as an exceptional drug candidate. Dr. Ho's claim that "there was little focus" on abacavir at the 1994 ICAAC conference is belied by the evidence. A news report of the conference's key presentations highlighted abacavir's positive results and discussed them as one of only four topics featured from among the numerous scientific reports. APO1060, 26:2:2; APO1025, 216:21-218:2; APO1067, ¶¶ 28, 67. Abacavir's positive preclinical results and its progression into clinical trials also would have encouraged a POSA to combine abacavir with AZT/3TC. APO1060, 26:2:2; APO1025, 216:21-218:2; APO1067, ¶¶ 27-29, 67.

5. ViiV ignores the significant disadvantages of PIs and NNRTIs.

ViiV argues that a POSA would have focused on PIs and NNRTIs for use in combination therapy. POR at 26-28. But ViiV ignores the many challenges associated with PIs and NNRTIs that were unresolved by March 1995. APO1067,

¶¶76-83. For example, PIs suffered from low bioavailability, complex synthesis protocols, low yield, long-term storage difficulties, expense, difficulty penetrating the CNS, and the need for frequent dosing. ViiV2035, 1. APO1067, ¶¶ 79-81. And as Dr. Ho admitted on cross-examination, "we already knew that [resistance] was going to be an issue with every single drug we developed" APO1071, 31:3-13. Similarly, Schinazi stated in February 1995 that "[t]he promise that protease inhibitors hold . . . *remains unfulfilled*" and "a significant reduction in bioavailability of certain protease inhibitors . . . has further dampened hopes for these compounds." APO1050, 46:1:4; APO1067, ¶¶79-81.

With regard to NNRTIs, a POSA would have been aware of the documented "rapid emergence" of NNRTI-resistant viruses within just a few weeks of treatment. ViiV2054, 67; APO1019, 214:1:3 and APO1067, ¶¶77-78. And many NNRTIs had poor oral bioavailability, requiring intravenous dosing. ViiV2003, PB0267; APO1019, 214; APO1067, ¶77. Additionally, as of March 1995, PIs and NNRTIs were much further behind in the development pipeline compared to NRTIs. APO1067, ¶¶77, 79, 82. As Schinazi explained "[n]o other class of antiviral agents has been studied more extensively" than NRTIs. APO1014, 155:1; APO1067, ¶75. And, in the year leading up to the March 1995 filing date, there had "been more clinical successes with nucleosides than with any other class of compounds." APO1050, 45:3:3; APO1014, 155; APO1067, ¶¶19-22, 72-77. Thus,

as of March 1995, an NRTI such as abacavir would have been a prime candidate for inclusion in a combination regimen. APO1067, ¶67.

6. Abacavir's resistance profile would have provided another reason to combine it with AZT/3TC.

ViiV argues that abacavir selects for the M184V mutation in HIV's reverse transcriptase enzyme and that this would have dissuaded a POSA from using abacavir. POR at 32. But contrary to ViiV's argument, abacavir's selection of the M184V mutation is *a reason to use abacavir as opposed to any other drug* in combination with AZT/3TC. APO2055, Abstract; APO1067, ¶¶35-42. As ViiV conceded and Dr. Ho admitted, "the M184V mutation sensitizes HIV to AZT." APO1071, 96:22-97:7; POR at 29; APO2055, Abstract; APO1067, ¶42. Using abacavir as part of a drug combination would thus increase the pressure on the virus to acquire and maintain the M184V mutation that makes the virus more sensitive to AZT. ViiV2006; ViiV2063, LB33; ViiV2055, 3-4; APO1067, ¶¶40-42; APO1071, 96:22-97:7. ViiV has not identified any other drug known as of March 1995 that would have provided similar selective pressure to maintain the M184V mutation to increase viral sensitivity to AZT, let alone a drug that also has all of the other favorable attributes of abacavir discussed herein. APO1067, ¶¶ 27-29, 67.

Though ViiV portrays resistance mutations as an insurmountable challenge,

the art recognized that "**[b]enefit may result even with development of mutations causing resistance,** either by greater reduction in viral load than with each agent given alone or by broadening the spectrum of specific cells and tissues in which antiretroviral agents act." ViiV2065, S33:2:4. Here, abacavir's resistance profile would not have dissuaded a POSA from combining it with 3TC and AZT. APO1067, ¶¶35-47.

Additionally, ViiV is wrong in asserting that the resistance profiles of abacavir and 3TC are "completely overlapping:" Dr. Ho admitted on cross-examination that he was not aware of specific mutations linked to 3TC resistance but not to abacavir resistance. ViiV2009, ¶89-96; APO1071, 99:13-100:12; APO1067, ¶47. In fact, researchers had linked certain reverse-transcriptase mutations to 3TC resistance but not to abacavir resistance. ViiV2073, 953:Fig.2; APO1043, 1391:1:2. APO1067, ¶47. Dr. Ho thus incorrectly asserted that abacavir and 3TC were known to have completely overlapping resistance profiles. ViiV2009, ¶89-96. APO1067, ¶47. A POSA would have viewed addition of abacavir as an advantageous way of preventing HIV from using these mutations as an alternative path to 3TC resistance. APO1067, ¶ 47. Accordingly, a POSA would have been motivated to add abacavir to the AZT/3TC combination because adding abacavir would help ensure that HIV could not escape the drugs by mutating residues that affect 3TC activity but not abacavir activity, and vice versa. *Id*.

Additionally, a POSA would have understood that cross-resistance between abacavir and 3TC (especially when used in combination with AZT) would take time to arise upon treating a patient with the combination of drugs. APO1067, ¶¶32-34. As discussed below in §B, the claims require no particular level of efficacy or duration of treatment. Thus, even if a POSA were concerned about development of cross-resistance, a POSA nonetheless would have had a reason to combine AZT, 3TC, and abacavir to provide clinical benefit for as long as possible in the face of a life-threatening disease. APO1067, ¶¶ 27-29, 67.

As of March 1995, a POSA would have had a reason to combine abacavir with AZT/3TC. APO1006, ¶¶ 52-54. AZT/3TC was the leading, "breakthrough" drug regimen upon which researchers sought to improve. APO1067, ¶17. in March 1995, researchers were developing triple-drug therapies, abacavir was known to possess the major positive attributes of a desirable drug candidate, and abacavir was further along in development than many other compounds that had been evaluated. APO1067, ¶¶77, 79. Given the seriousness of the AIDS crisis in March 1995, a POSA would have had a reason to combine AZT, 3TC, and abacavir. APO1006, ¶¶ 52-54; APO1067, ¶¶15-29.

B. ViiV did not rebut a POSA's reasonable expectation of success.

As of March 1995, a POSA would have had a reasonable expectation of success in arriving at the claimed invention by adding abacavir to the AZT/3TC

combination. APO1006, ¶¶49, 54; APO1067, ¶¶ 6, 29, 45, 100. ViiV's fears of toxicity and cross-resistance amount to unsupported speculation that does not refute a POSA's reasonable expectation of success. APO1003; APO2006 I82, I84, I86, I88; ViiV2024, 8; APO1067, ¶¶ 35-47, 53-56, 72-75. ViiV cites no evidence reporting unacceptable toxicity for AZT, 3TC, or abacavir, alone or in combination. And, the AZT/3TC combination had already been demonstrated to safely and successfully treat HIV, so a POSA would have reasonably expected that adding abacavir—which was safe and effective in its own right—would provide a combination that also could successfully treat or prevent the symptoms or effects of HIV. APO1013; APO1006, ¶54; APO1067, ¶¶ 27-29. None of ViiV's evidence refutes the positive attributes a POSA would have expected to result from the claimed combination. For example, none of ViiV's evidence shows that abacavir is antagonistic with AZT, 3TC, or even "any other NRTI." APO1071, 101:11-17. APO1067, ¶60, 88. So ViiV's toxicity arguments fail.

ViiV's cross-resistance arguments likewise fail. As discussed above, ViiV and Dr. Ho are wrong to assert that abacavir and 3TC have "completely overlapping" resistance profiles. APO1067, ¶¶46-47. And abacavir's mutational profile was known to make the virus *more* sensitive to AZT. APO1067, ¶42. Thus, a POSA would have reasonably expected the combination of AZT, 3TC, and abacavir to be successful in treating or preventing the symptoms or effects of HIV

as claimed. Additionally, ViiV's arguments regarding cross-resistance should be disregarded because they are inapposite to the challenged claims. As discussed above, cross-resistance gradually and incompletely arises in patients over the course of time in treating a patient. APO1067, ¶¶32-34, 40. As ViiV's expert admitted on cross-examination, the challenged claims do "not specify any particular level of efficacy" or "any particular duration of efficacy." APO1071, 55:5-25; APO1067, ¶¶34, 106. Accordingly, the prior art renders the claims obvious even if one would have expected cross-resistance eventually to arise.

Likewise, the prior art renders the claims obvious even if there were some uncertainty as to whether the combination would be more efficacious than preexisting regimens, since the claims do not require any particular level of efficacy—let alone improvement over preexisting regimens. To the extent ViiV contends that the prior art must have rendered obvious a drug regimen that was *improved* over preexisting regimens, ViiV has improperly imported a limitation into the claims. APO1067, ¶¶32-34, 106. Though ViiV provides no claim construction of its own, ViiV criticizes Apotex's claim construction by asserting that "the only motivation in the field was to improve upon the prior art..." (POR at 8; emphasis omitted). But for the reasons discussed above, the claims do not require any such improvement. APO1067, ¶¶32-34, 106. Given the art-recognized success of the AZT/3TC combination, and given abacavir's favorable

characteristics and positive interactions with each of AZT and 3TC, a POSA would have had a reasonable expectation of success in making a therapeutically effective combination of drugs as claimed. APO1067, ¶¶ 17-29.

C. ViiV's attempts to show objective indicia of nonobviousness fail.

ViiV has not presented evidence of commercial success. ViiV's commercial success arguments are flawed from the outset because (i) they rely on hearsay and attorney argument, and (ii) Dr. Ho admittedly is not an expert in economics or pharmaceutical markets. POR at 38-41; APO1071, 105:10-106:13. Moreover, ViiV and Dr. Ho did not account for the existence of blocking patents, and Dr. Ho conducted no analysis of the marketplace for HIV therapeutics. APO1071, 105:10-106:13. In view of such shortcomings in its evidence, ViiV has not met its burden of production to establish commercial success.

Unlike Dr. Ho, Apotex's expert, Dr. Hofmann, analyzed the prescription data for ATZ, 3TC, abacavir, and combinations thereof, and shows that Epzicom® and Trizivir® merely cannibalized sales of the existing individual component drugs known in the art. APO1069, ¶¶8, 21, 32-43. In other words, Epzicom® and Trizivir® did not exhibit commercial success arising from a novel feature of the claims. *Id.* Rather, it was the individual drug components, already known in the prior art, that accounted for the sales of the products. *Id.*; APO1006, ¶142.

Furthermore, the presence of blocking patents covering the component drugs

of the challenged claims negates any indicia of nonobviousness that might be present in the sales data. APO1067, ¶¶ 98-103; APO1069, ¶¶8, 21-31; *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005). As Dr. Hoffman explains, ViiV's predecessor held rights to blocking patents that prevented competition in the marketplace for many years. EX1034 at 62; APO1069, ¶¶23-27. Notably, the market entry of both Trizivir® and Epzicom® occurred after ViiV and its predecessors secured the rights to all of the Blocking Patents, which distorts the sales results for both Trizivir® and Epzicom®. *Id.* Dr. Ho and ViiV do not account for the existence of such Blocking Patents, nor do they account for marketing, advertising, or other factors that affect the sales of a product. *Id.*, ¶¶33, 43. And Epzicom® and Trizivir® gained only minor shares (4.9% and 5%), of the overall anti-HIV therapeutic market. *Id.*, ¶¶43-45; APO1025, 267:16-268:4. ViiV fails to demonstrate that even this minor share is due to any alleged novel feature of Epzicom® or Trizivir®. APO1069, ¶¶8, 34-42. For example, ViiV does not show why physicians prescribe Epzicom® or Trizivir®, and ViiV fails to establish a nexus between the sales and any particular feature of the claims. *Id.*

ViiV has not presented evidence of unexpectedly superior results. ViiV argues that without actually testing a combination a POSA could not reasonably predict how it would perform *in vitro*. POR at 30. So under ViiV's logic, no

prediction could be made and *any* result would have been unexpected. But ViiV does not dispute that many different combinations of NRTIs showed synergy when tested *in vitro*, including AZT/3TC and AZT/abacavir. APO1002, Fig. 1; APO1003; APO1006, ¶¶124-1230; APO1019, 223; APO1067, ¶¶ 59-60. Moreover, a showing of unexpected results requires unexpectedly superior results compared to the closest prior art. Pet. at 39. Yet Dr. Ho admittedly did not even "form an opinion as to what is the closest prior art." APO1071, 102:9-17. ViiV's arguments for unexpected *in vitro* results are flawed *ab initio*. APO1067, ¶¶84-90.

ViiV alleges certain examples of drugs did not show synergy in the three-drug context. ViiV2009, ¶113. But ViiV's examples would not have been relevant to a POSA in determining whether the claimed invention provides *unexpectedly* superior results because those data all come from a *confidential* report compiled *nine years after* the effective filing date, and thus would not have been known to a POSA at the time of the invention. APO1067, ¶60; ViiV2009, ¶113.

And a POSA would not have considered the clinical data ViiV discusses to be evidence of unexpected results. None of the reports ViiV cites can show unexpectedly superior results because they at most show only a marginal improvement over the art. APO1067, ¶¶91-97; APO1020; ViiV2094; ViiV2007; ViiV2009, 65 (conceding in FN13 that the clinical studies Dr. Ho cites are "designed to show equivalence"). For instance, the PENTA studies showed at best

"a slight and statistically non-significant difference in HIV RNA suppression" by 3TC/abacavir, while Sáez-Llorens only showed "modest" viral suppression by AZT/3TC/abacavir. APO1067, ¶¶91-96; ViiV2094, 736:Fig. 2; ViiV2009, 950:Fig. 2; APO1021, 8:1:3-8:2:1. ViiV also argues that the results with the claimed combinations were unexpected relative to combinations other than the closest prior art, but comparisons with something other than the closest prior art are irrelevant. Pet. at 39; POR at 46; APO1033; APO1067, ¶¶94-97. And ViiV makes the legally erroneous assertion that a study showing results "non-inferior to AZT/3TC was still a superior result." POR at 45.

ViiV cites only one clinical study comparing abacavir/AZT/3TC to AZT/3TC and concedes that the addition of abacavir caused only a modest response. POR at 46. ViiV also notes that a greater proportion of the patients on the triple therapy showed HIV-1 RNA levels of <10,000 copies/ml. *Id.* But ViiV does not show how that result was unexpected given abacavir's known, potent antiviral activity. APO1067, ¶¶ 91-97. As discussed above, a POSA would have expected that adding abacavir to the proven AZT/3TC combination would increase observed antiviral effects. APO1067, ¶¶ 17-29. As Dr. Johnson explains, "three-drug regimens delay breakthrough of HIV-1 replication more effectively than two-drug regimens or single-drug regimens." APO1004, 908:1:2; ViiV2065, S25:1:3.

ViiV has not demonstrated that the claimed invention met a long-felt

but unmet need. ViiV agrees the combination of AZT/3TC was a "breakthrough" and significantly increased patient survival. APO1067, ¶17; APO1012; APO1071, 32:15-33:3. Yet ViiV alleges there was a need for "less toxic therapies that delayed resistance even longer." But ViiV fails to show any nexus to the claims of the '191 patent, and ViiV fails to show that the claimed invention is less toxic than, or has delayed resistance compared to, the AZT/3TC treatment. APO1067, ¶¶ 106-107. Thus, ViiV's long-felt-need arguments fail.

ViiV has not presented evidence of industry praise. ViiV's industry praise arguments are flawed because the "treatment guidelines" ViiV offered do not amount to industry praise. POR at 47-48; ViiV2009, ¶145; APO1067, ¶105. The CAFC has rejected evidence of "efficacy" and "indications," noting that it "fall(s) well short of demonstrating true industry praise." *Bayer Healthcare v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). Accordingly, ViiV's evidence of treatment guidelines cannot amount to praise in the industry. *Id.*

Moreover, "praise for an invention by peers in the industry may support nonobviousness, but only if the such praise is directed to the claimed invention and *not to elements found in the prior art*." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1365-66 (Fed. Cir. 2007). ViiV does not dispute that the AZT/3TC combination and abacavir were known in the prior art. APO1002; APO1003. Therefore, even if treatment guidelines were considered praise—and

they are not—they relate only to elements known in the art. APO1067, ¶105.

ViiV has not presented evidence of skepticism of others. ViiV cites to ViiV2004 as evidence for concern about the combination of abacavir and 3TC, but that paper was published in 1993 and does not mention abacavir. POR at 49. ViiV states "the committee express;yconcerned [sic] the claimed combination of abacavir and 3TC." POR at 50. But ViiV offers no evidence for skepticism regarding the three drug combination of abacavir/AZT/3TC. APO1067, ¶104. Accordingly, ViiV's evidence is not commensurate in scope with any of the challenged claims, including the two-drug claims, which can include additional drugs, like AZT. Pet. at 22-23. And even accepting ViiV's evidence at face value, the fear of cross-resistance between abacavir and 3TC would not have applied to the three-drug combination as discussed above in § I.A.6. Indeed a POSA would not have had significant concerns about cross resistance between abacavir and 3TC, especially when used with AZT. APO1067, ¶¶35-47. Further, any concerns regarding the potency or duration of effect of the invention do not share a nexus with claims that require neither a specific potency nor a specific duration. APO1067, ¶¶32-34, 107; ViiV2094, 738:2:4.

II. ViiV's separate patentability arguments fail.

Claim 4 - ViiV argues that determining "optimum ratios" of the three drugs required "actual testing." POR at 51. But such testing would have been routine to a

POSA. APO1006, ¶61; APO1067, ¶¶116-117. Moreover, ViiV concedes that the prior art discloses ranges of each of the three drugs that overlaps with the claimed range. POR at 51. That the ranges disclosed in Cameron and Daluge overlap the range of ratios recited in claim 4 establishes a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). And ViiV has not established that the range recited in claim 4 (or any other claim) is critical or provides any unexpected results. POR at 51; ViiV2009, ¶¶170-172.

Moreover, a POSA would have had significant guidance regarding the appropriate dose based on the art. APO1002, 5:38-57; APO1003; APO1006, ¶¶56-72, 88-89, 102-107. Dr. Ho uses Daluge's high and mid-range doses as a basis to show some of the ratios disclosed in Cameron would fall outside the claimed range. ViiV2009, ¶172. But ViiV and Dr. Ho fail to acknowledge that Daluge's high and mid-range doses were used in toxicity tests in animals and are much higher than a POSA would have used to treat a human. POR at 51; APO1002; APO1003, I6; APO1067, ¶ 116.

The single, combined formulation claims - ViiV argues that use of a single, combined formulation would not have been obvious because of intracellular half-life differences between abacavir (3.3 hr) and 3TC (10 to 15 hr). ViiV1009, ¶¶174, 175. But ViiV does not point to any exhibit discussing the intracellular half-life of 3TC. But even if ViiV had provided support, a POSA would not have been

deterred from combining drugs with different intracellular half-lives. APO1067, ¶¶27-29, 67. For example, AZT's intracellular half-life was known to be one hour, yet it was still combined with 3TC. APO1073, 1692:2:1; ViiV2009, ¶174.

III. The District Court did not consider Cameron combined with Daluge.

Contrary to ViiV's portrayal, the district court did not consider the art Apotex presents here. POR at 4-5. The district court referred to Daluge (APO1003) only to *specifically exclude it from consideration* because of defendant's (Teva's) procedural violation. APO1034, 44. And the opinion does not even mention Cameron (APO1002). APO1034. Thus, the district court's failure to invalidate the '191 patent is of no moment, and the CAFC's rule 36 affirmance does not preclude the Board from reaching a different conclusion in light of this evidence.

IV. Conclusion

Nothing ViiV argued should alter the Board's initial views regarding unpatentability. Apotex has demonstrated obviousness of claims 1-51 by at least a preponderance of the evidence.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Eldora L. Ellison /
Eldora L. Ellison
Registration No. 39,967
Attorney for Petitioner

Date: June 15, 2015
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned "Apotex Corp.'s Reply to Patent Owners ViiV Healthcare Co. and ViiV Healthcare UK LTD.'s Response to the Petition" was served in its entirety on June 15, 2015, upon the following parties via email.

PATENT OWNER VIIV HEALTHCARE UK LTD

F. Christopher Mizzo
Charles A. Fernández
Kirkland & Ellis LLP
655 Fifteenth Street, N.W.
Suite 1200
Washington, D.C. 20005
Telephone: (202) 879-5236
Facsimile: (202) 654-9607
cmizzo@kirkland.com
cfernandez@kirkland.com
ViiVKirklandETIPRService@kirkland.com

Eugene Goryunov (Reg. No. 61,579)
Kirkland & Ellis LLP
300 North LaSalle
Chicago, IL 60654
Telephone: (312) 862-7059
Facsimile: (312) 862-2200
egoryunov@kirkland.com

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Eldora L. Ellison/

Date: June 15, 2015

Eldora L. Ellison (Reg. No. 39,967)
Lead Attorney for Petitioner Apotex Corp.
1100 New York Avenue, N.W.
Washington, D.C. 20005 - 3934
(202) 371-2600