Case Summary
1/12

This case will help you understand:

How GlaxoSmithKline (GSK) drugs containing abacavir (ABC) were discovered to induce hypersensitivity in a small number of patients.

How the hypersensitivity scare meant that Gilead's Truvada was able to capture a bigger share of the market.

How hands-on use studies, to demonstrate unequivocally the role of the test in eliminating the abacavir hypersensitivity problem, helped to restore Epzicom's revenue growth.

Key messages:

GSK initiated a prospective study that showed a pharmacogenetic test can be used to prevent a specific toxic effect from a drug.

GSK prepared a major marketing offensive for the US to encourage adoption of the test.

The demand for testing grew rapidly in the US after the campaign was launched and Epzicom's revenue growth resumed after a 4-6 month hiatus.

Key actions:

Understand the role of hands-on use studies.

Consider how a hands-on use study could support demand for your Dx.

Consider how proactive promotion of the benefits of testing would support your therapy.

Epzicom is Indicated for the Treatment of HIV-1 Infection
2/12

-----INDICATIONS AND USAGE-----

Epizicom, a combination of abacavir and lamivudine, both nucleoside analogue HIV-1 reverse transcriptase inhibitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Source: http://www.accessdata.fda.gov

So What?

The challenge: GSK drugs containing abacavir (ABC) were discovered to induce hypersensitivity in a small number of patients.

Commentary

In August 2004, the Food and Drug Administration (FDA) approved two competing fixed-dose combination treatments for HIV-1 infection: Epzicom (abacavir/lamivudine), from GSK, and Truvada (tenofovir disoproxil/emtricitabine), made by Gilead.

Shortly after Epzicom's launch, patients and physicians began reporting that some patients experienced hypersensitivity reactions to abacavir. This manifested as flu for a small number of patients. The patients suffered no long-term effects, provided they stopped taking ABC.

In July 2006, the FDA placed a black box warning on Epzicom in the US, highlighting the hypersensitivity issue.

The Challenge
3/12

What is Abacavir Hypersensitivity Reaction (HSR)?

- Fever
- Rash
- Gastro Symptoms
- Constitutional Symptoms

Abacavir is Ziagen and a component in Epzicom & Trizivir

Source: http://www.gsk.com/

So What?

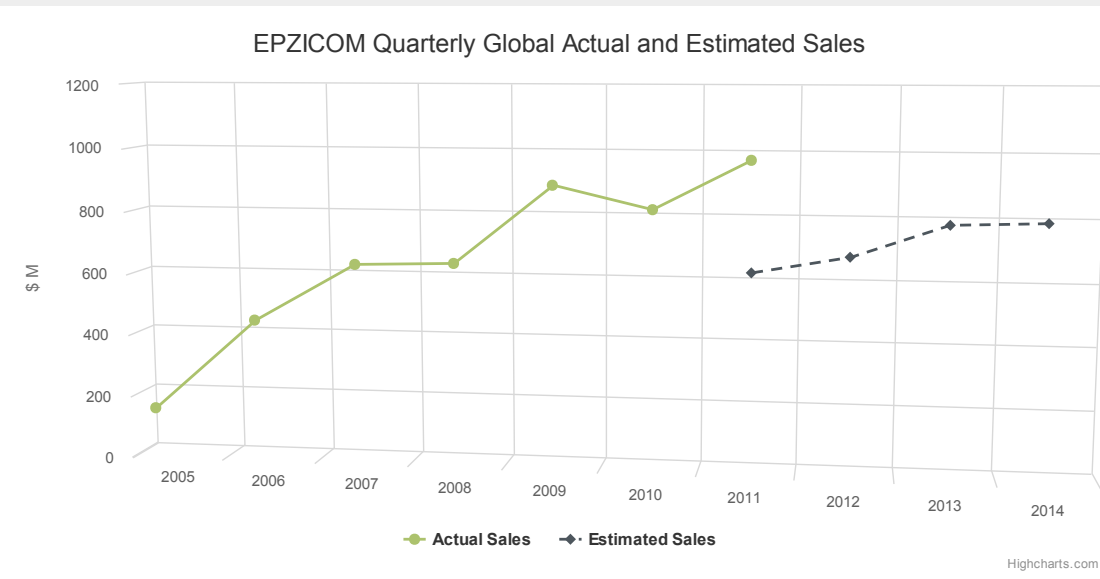
The problem: The hypersensitivity scare meant that Gilead's Truvada, which had an issue-free launch, was able to capture 75 per cent of the market by July 2007, up from 50 per cent a year earlier.

Commentary

The timeline of events indicates that GSK identified an association of the HLA-B*5701 allele with the abacavir hypersensitivity reaction in 2001. The association was not fully understood until the end of 2003, when LabCorp began offering an HLA-B*5701 test.

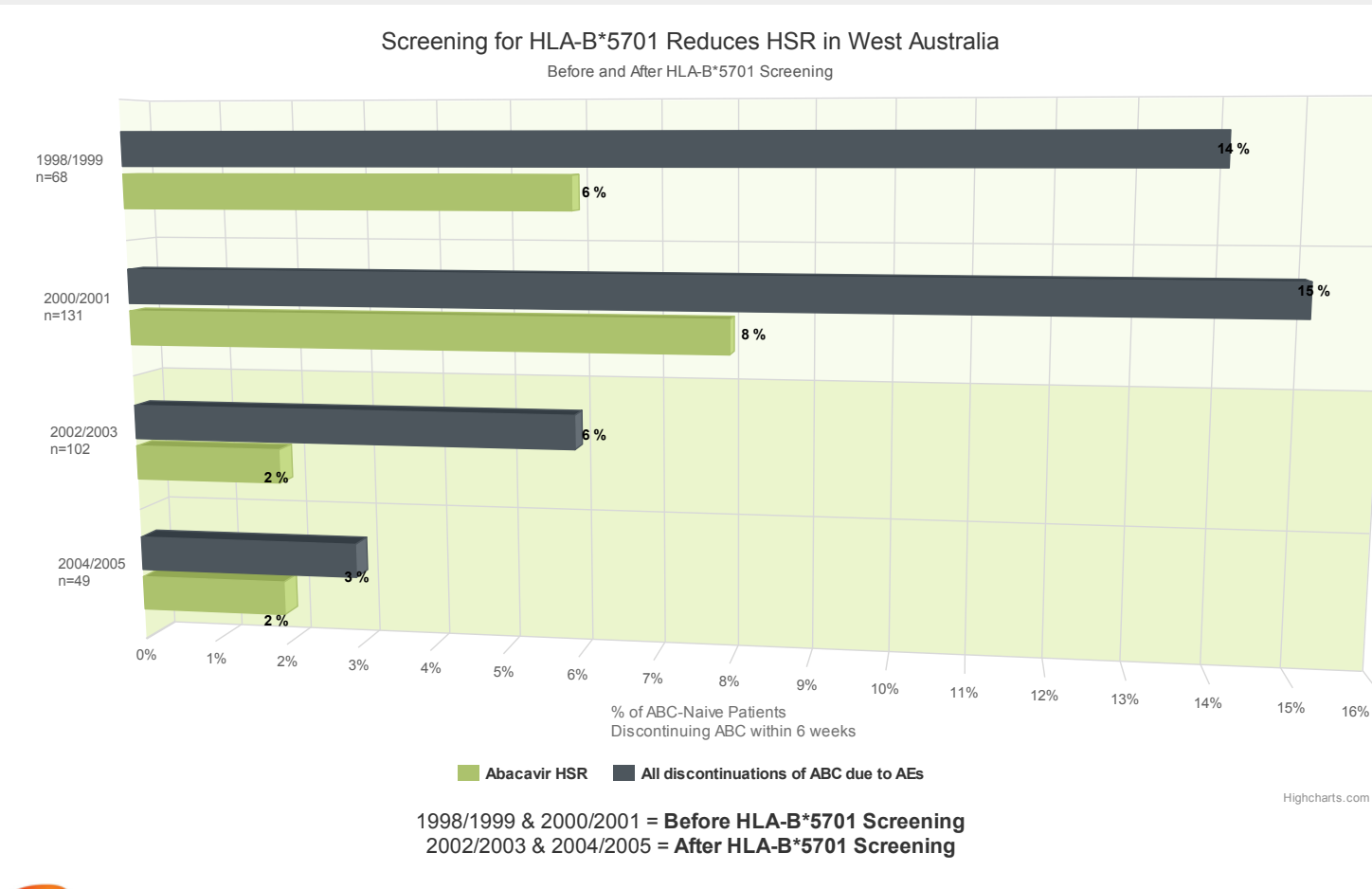
However, demand in the US for the test was low (20 to 30 requests per year). The lack of awareness about the test, combined with the FDA's 2006 black box warning for ABC-containing drugs, meant that GSK's ABC portfolio, including Epzicom, began to plateau and lose sales.

The Problem
4/12



Source: http://www.nature.com

HLA-B*5701 Screening (1)
5/12


Screening for HLA-B*5701 Reduces HSR in West Australia
Before and After HLA-B*5701 Screening
1998/1999
n=68
14 %
6 %
2000/2001
n=131
15 %
8 %
2002/2003
n=102
6 %
2 %
2004/2005
n=49
3 %
2 %
0%
1%
2%
3%
4%
5%
6%
7%
8%
9%
10%
11%
12%
13%
14%
15%
16%
% of ABC-Naive Patients
Discontinuing ABC within 6 weeks
Abacavir HSR
All discontinuations of ABC due to AEs
Highcharts.com
1998/1999 & 2000/2001 = Before HLA-B*5701 Screening
2002/2003 & 2004/2005 = After HLA-B*5701 Screening
gsk GlaxoSmithKline

Source: http://www.gsk.com/investors/presentations/2007/roundtable07/hare-09172007-roundtable.pdf

HLA-B*5701 Screening (2)
6/12

Countries that Routinely Test have Higher ABC Market Shares

	Epzicom/Kivexa Share	ABC-Containing Products Share	% of Physicians Using Test
US	8%	18%	<6%
UK	17%	24%	70%
Australia	16%	22%	>50%

GlaxoSmithKline

Source: http://www.gsk.com/investors/presentations/2007/roundtable07/hare-09172007-roundtable.pdf Show Associated Resources

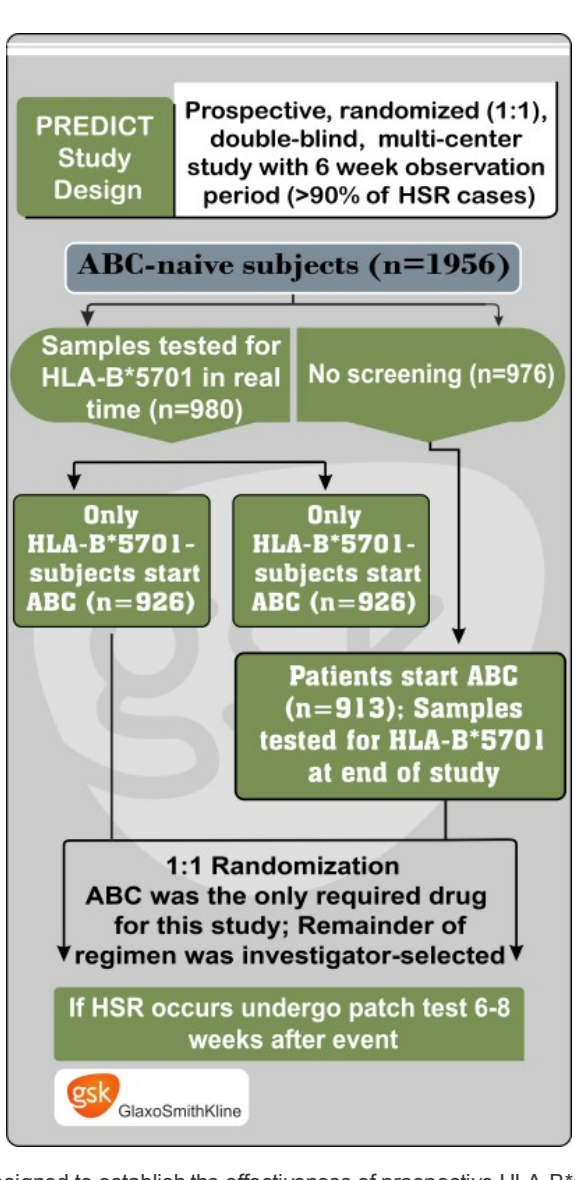
So What?

To demonstrate unequivocally the role of the test in eliminating the abacavir hypersensitivity problem, GSK initiated a prospective study in 2006, the results of which were published in the New England Journal of Medicine in February 2008.

Commentary

GlaxoSmithKline began a prospective study in 2006 to determine the benefit of HLA-B*5701 testing in helping to screen out patients who were hypersensitive to abacavir.

The PREDICT Study
7/12


PREDICT Study Design
Prospective, randomized (1:1), double-blind, multi-center study with 6 week observation period (>90% of HSR cases)
ABC-naive subjects (n=1956)
Samples tested for HLA-B*5701 in real time (n=980)
No screening (n=976)
Only HLA-B*5701-subjects start ABC (n=926)
Only HLA-B*5701-subjects start ABC (n=926)
Patients start ABC (n=913): Samples tested for HLA-B*5701 at end of study
1:1 Randomization
ABC was the only required drug for this study; Remainder of regimen was investigator-selected
If HSR occurs undergo patch test 6-8 weeks after event
gsk GlaxoSmithKline

The PREDICT study was designed to establish the effectiveness of prospective HLA-B*5701 screening to prevent the hypersensitivity reaction to abacavir. The data from the PREDICT study along, with other retrospective trial data, were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) and International AIDS Society meeting in June 2007, and published in the New England Journal of Medicine in February 2008.

The double-blind, prospective, randomized PREDICT study involved 1956 patients from 19 countries, who were infected with human immunodeficiency virus type 1 and who had not previously received abacavir. The team randomly assigned patients to undergo prospective HLA-B*5701 screening, with exclusion of HLA-B*5701–positive patients from abacavir treatment (prospective-screening group), or to undergo a standard-of-care approach of abacavir use without prospective HLA-B*5701 screening (control group). All patients who started abacavir were observed for six weeks. The team performed epicutaneous patch testing with the use of abacavir.

The trial found that the HLA-B*5701 allele was present in 5.6 per cent of patients (109 of 1956 patients). Of the patients receiving abacavir, 72 per cent were men, 84 per cent were white, and 18 per cent had not previously received antiretroviral therapy. Screening eliminated immunologically-confirmed hypersensitivity reaction (0 per cent in the prospective-screening group versus 2.7 per cent in the control group, P<0.001), with a negative predictive value of 100 per cent and a positive predictive value of 47.9 per cent. The hypersensitivity reaction was clinically diagnosed in 93 patients, with a significantly lower incidence in the prospective-screening group (3.4 per cent) than in the control group (7.8 per cent).

The study concluded that HLA-B*5701 screening reduced the risk of a hypersensitivity reaction to abacavir. It showed that in populations similar to the predominantly white group in the study, 94 per cent of patients do not carry the HLA-B*5701 allele and are at low risk for hypersensitivity reaction to abacavir.

Ultimately, the study showed that a pharmacogenetic test can be used to prevent a specific toxic effect from a drug.

Source: http://www.gsk.com/investors/presentations/2007/roundtable07/hare-09172007-roundtable.pdf

So What?

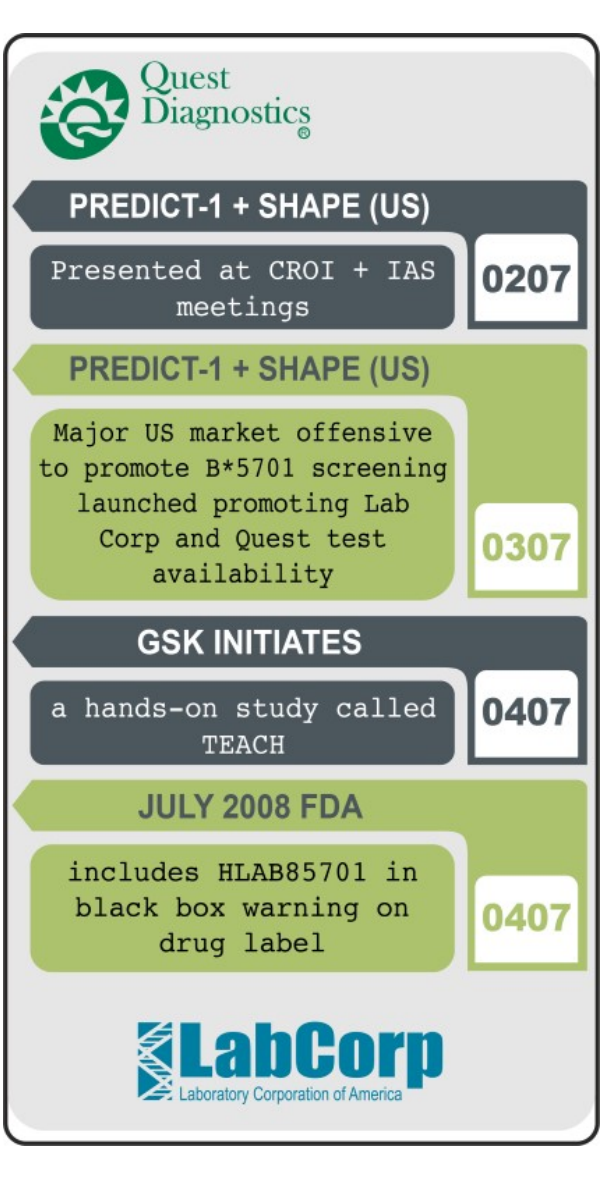
GSK launched a major marketing offensive in August 2007, recommending that all HIV patients be tested.

Commentary

Throughout the early part of 2007, GlaxoSmithKline prepared a major marketing offensive for the US, timed to commence with the presentation of the PREDICT data at CROI and other HIV conferences. GSK would recommend that every HIV patient know his or her HLA-B*5701 status. In addition, GSK collaborated with Quest and LabCorp to ensure their HLA-B*5701 tests were widely available and priced at a rate that would not create a barrier to testing.

To help encourage adoption of the test, GSK launched a "hands-on use" or observational study in the third quarter of 2007. The study offered potential prescribers the opportunity to run ten tests each on patients and report the results. The study also enabled GSK to ensure that providers were able to conduct the tests easily. (The effectiveness of hands-on use studies is discussed in more detail in the clinical framework presentation.)

Marketing Offensive
8/12


Quest Diagnostics
PREDICT-1 + SHAPE (US)
Presented at CROI + IAS meetings
0207
PREDICT-1 + SHAPE (US)
Major US market offensive to promote B*5701 screening launched promoting Lab Corp and Quest test availability
0307
GSK INITIATES
a hands-on study called TEACH
0407
JULY 2008 FDA
includes HLAB85701 in black box warning on drug label
0407
LabCorp
Laboratory Corporation of America

So What?

To enable the promotion of the HLA-B*5701 test, which was not FDA-approved, GSK agreed with the FDA that it would be incorporated into the black box warnings for drugs containing abacavir.

Commentary

Interestingly, although the HLA-B*5701 test was not FDA-approved, the FDA supported the test because of its role as a safety biomarker. The test, which was available as a lab-developed test from LabCorp and Quest, was incorporated into the black box section of all abacavir-containing drug labels in July 2008.

As GSK noted in its release, "FDA Approves Updated Labelling for Ziagen": "The US Food and Drug Administration (FDA) has approved GlaxoSmithKline's request to add new language to the prescribing information for its HIV nucleoside-reverse transcriptase inhibitor (NRTI) Ziagen (abacavir sulfate). The newly added information recommends taking into consideration two separate factors in prescribing decisions: patients' HLA-B*5701 allele status and underlying heart disease risk factors when prescribing antiretroviral therapies including abacavir."

Other Planning Issues
9/12

FDA Approves Updated Prescribing Information for Abacavir (Ziagen, Epzicom and Trizivir)

This week GlaxoSmithKline (GSK) and the US Food and Drug Administration (FDA) announced new updated label information for the nucleoside reverse transcriptase inhibitor abacavir (Ziagen). Abacavir is also a component of the fixed-dose combination pills Epzicom (abacavir + lamivudine [3TC]) and Trizivir (abacavir + lamivudine + Zidovudine [AZT]).

Warnings

EPZICOM contains 2 nucleoside analogues (abacavir sulfate and lamivudine) and is intended only for patients whose regimen would otherwise include these 2 components.
Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of EPZICOM. Hypersensitivity to abacavir is multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) Constitutional (including generalized malaise, fatigue or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.
Regardless of HLA-B*5701 status, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Source: http://www.rxlist.com/epzicom-drug.htm

So What?

The demand for testing grew rapidly in the US after the campaign was launched and Epzicom's revenue growth resumed after a 4-6 month hiatus.

Commentary

The immediate impact of the marketing program was to reinstate growth for Epzicom in the US. Diaceutics estimates that over the first nine months of the program, GSK added at least an additional $30m in revenue which would otherwise have been lost.

Demand for Testing
10/12

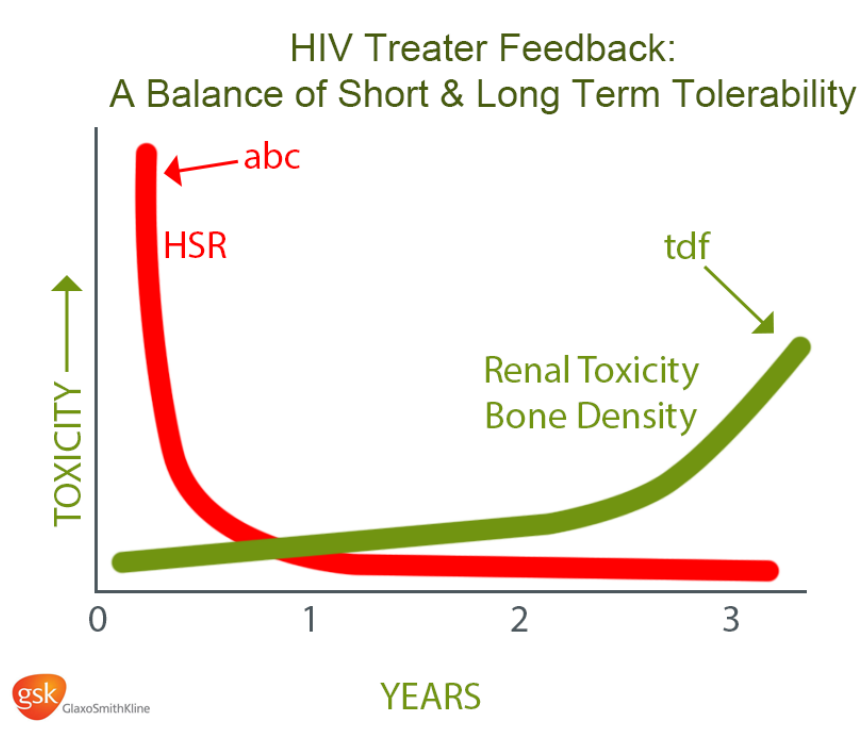
So What?

GSK also used the diagnostic market to turn a defensive strategy into an offensive strategy against Epzicom's nearest competitor, Tenofovir, which had long-term toxicity issues not previously focused on by physicians.

Commentary

In addition to proactively promoting the benefits of testing for abacavir-containing drugs, GSK produced educational materials that highlighted the benefits of testing for liver function and bone density. Such tests put competitor products with potential long-term toxicity issues at a disadvantage. With this action, GSK leveraged the full advantages of interacting with the diagnostic market.

HIV Treater Feedback
11/12



Source: http://www.gsk.com/investors/presentations/2007/roundtable07/hare-09172007-roundtable.pdf

Key Messages
12/12

Key messages:

GSK initiated a prospective study that showed a pharmacogenetic test can be used to prevent a specific toxic effect from a drug.

GSK prepared a major marketing offensive for the US to encourage adoption of the test.

The demand for testing grew rapidly in the US after the campaign was launched and Epzicom's revenue growth resumed after a 4-6 month hiatus.

Key actions:

Understand the role of hands-on use studies.

Consider how a hands-on use study could support demand for your Dx.

Consider how proactive promotion of the benefits of testing would support your therapy.