MAJOR ARTICLE

The Successful Application of a National Peer Advisory Committee for Physicians Who Provide Salvage Regimens to Heavily Antiretroviral-Experienced Patients in Mexican Human Immunodeficiency Virus Clinics

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Background. Designing optimal antiretroviral (ARV) salvage regimens for multiclass drug-resistant, human immunodeficiency virus (HIV)-infected patients demands specific clinical skills. Our aim was to assess the virologic and immunologic effects of the treatment recommendations drafted by a peer advisory board to physicians caring for heavily ARV-experienced patients.

Methods. We conducted a nationwide, HIV clinic-based, cohort study in Mexico. Adults infected with HIV were assessed for a median of 33 months (interquartile range [IQR] = 22–43 months). These patients had experienced the virologic failure of at least 2 prior ARV regimens and had detectable viremia while currently being treated; their physicians had received therapeutic advice, by a panel of experts, regarding the ARV salvage regimen. The primary endpoint was the incidence of loss of virologic response (plasma HIV-RNA levels of <200 copies per mL, followed by levels above this threshold) during the follow-up assessment using an observed-failure competing risks regression analysis.

Results. A total of 611 patients were observed (median ARV therapy exposure = 10.5 years; median prior regimens = 4). The probabilities of virologic failure were 11.9%, 14.4%, 16.9%, and 19.4% at the 12-, 24-, 36-, and 48-month follow-up assessments, respectively. Of the 531 patients who achieved a confirmed plasma HIV-RNA level below 200 copies per mL, the median increase in blood $CD4^+$ T-cell count was 162 cells per mL (IQR = 45–304 cells per mL).

Conclusions. In routine practice, a high rate of patients with extensive ARV experience, who received an optimized salvage regimen recommended by a peer advisory committee, achieved a long-term sustained virologic response and immune reconstitution.

Keywords. antiretroviral; HIV; Mexico; peer advice; resistance.

The proportion of triple-class antiretroviral (ARV) therapy-experienced patients infected with multidrug-resistant (MDR) human immunodeficiency virus (HIV)-1 variants is significant in routine clinical care settings [1–8]. These individuals are at a higher risk of clinical progression and death [9–11], and they are a potential source of transmission and dissemination of MDR viral strains.

Several randomized clinical trials [12, 13] have demonstrated that new ARV agents with expanded activity (XA-ARV) within existing (tipranavir, darunavir, and etravirine) and novel classes (raltegravir, enfuvirtide, and maraviroc) are often the cornerstone of the salvage regimens that lead to high rates of maximally sustained virologic suppression among patients. Nevertheless, there is still a need for observational studies to assess

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whether these promising results from highly motivated study participants and physicians are generalizable to routine general clinical practice.

Strong prescriber adherence to a series of basic therapeutic principles is crucial to achieve optimal outcomes and avert the emergence of viral resistance to new agents [14]. These principles include the accurate prediction of drug antiviral activity via a thorough review of patients' complete treatment histories, the correct interpretation of resistance tests, the assessment of potential drug–drug interactions, and the inclusion of at least 2 (preferably 3) fully active agents in the drug regimen [15]. Strict compliance with these principles can be difficult to achieve among nonexperienced practitioners, and prescribing errors might cause new salvage regimens to fail.

In 2001, the Mexican Ministry of Health launched a nationwide scale-up of the universal ARV free-access program [16]; by 2013, ~57 000 patients had been enrolled [17]. Most of the prescribers in this program are general physicians with <3 years of experience in treating patients with HIV [18]. In 2008, the Ministry of Health created a national board of clinicians with several years of experience in ARV therapy to aid Mexican physicians in prescribing deep salvage regimens that are likely to be successful in heavily treatment-experienced patients and optimizing the use of the new XA-ARV drugs in routine clinical care.

The current study aims to assess the virologic and immunologic effects of the salvage regimen recommendations provided to physicians by the Mexican ARV therapy peer advisory committee in a cohort of patients with extensive ARV treatment experience and multiple treatment failures.

PATIENTS AND METHODS

Sample

The eligibility criteria required that patients were (1) considered cases of ARV-virologic failure (ongoing viral replication as defined by an HIV viral load of more than 500 copies/mL in at least 2 prior consecutive measurements) and were receiving ARV therapy at the time of the committee assessment; (2) 18 years or older; and (3) under the care of a physician who received and complied with the therapeutic recommendations of the salvage regimen provided by the Mexican Advisory Board for Rational Antiretroviral Usage (*Comité para el Uso Racional de los Antirretrovirales* [CORESAR]). Patients were assessed for at least 12 months after the start of the recommended ARV salvage regimen. The participants included in the study were previously examined by the CORESAR between November 2008 and February 2012.

Intervention

The peer advisory process is composed of 3 steps. In the first step, the physician completed a structured application form. This form collects data concerning patient plasma HIV-1 RNA (vRNA) plasma viral load measurements, $CD4^+$ T-cell counts, coinfections, clinical events, concurrent medications (other than ARVs), a complete history of ARV therapy, and the reasons for drug changes (eg, virologic failure, adverse events, non-adherence, regimen simplification, or pharmacologic interactions) since the HIV-infection diagnosis. The second step involved the individual assessment of patients by a panel of 10 senior clinicians with sound experience in ARV therapy. Based on the collected data (including resistance testing: HIV genotyping for 93% of all patients), each member of the CORESAR (independent of the other members) proposed an optimized salvage regimen. These members sought to include at least 2 (preferably 3) fully active agents in the suggested drug regimen whenever possible. The third step was providing the committee's final recommendation and the rationale for this advice to the clinician caring for the patient. This recommendation was decided by consensus among the board members via a case-by-case analysis and a discussion at a plenary meeting. Drugs such darunavir, raltegravir, etravirine, and maraviroc were stored at the board's pharmacy and were not freely available to the treating physicians; these drugs were sent to the HIV clinic when they were included in the recommended regimen. The remaining ARV drugs were dispensed through the regular federal ARV open-access system. The peer advisory committee task was to recommend the optimal drug regimen in cases with lack of viral control (associated with drug resistance) regardless of the cause of virologic failure.

Surveillance

After the optimized salvage regimen was initiated, vRNA viral load measurements, $CD4^+$ T-cell counts, and the mortality rate were recorded. The follow-up assessment was accomplished by reviewing the prescription data from the national database designed by the ARV governmental program. Clinicians populate the data in this electronic system, which is used to monitor ARV prescriptions of the patients cared for by the Ministry of Health, and its use is compulsory for practitioners who belong to this program. Whenever necessary, the investigator conducted direct interviews with the practitioners. The follow-up assessment ended on August 15, 2013 (the time of analysis). The start date of the salvage regimen was retrieved from the database.

Virologic Response Definitions

1. Response: complete follow-up assessment. Participants included in this category were those who, at the end of the follow-up assessment (March to August 2013), had a confirmed (ie, 2 consecutive measures) vRNA level below 200 copies per mL. The time of sustained virologic response was defined as the time from the start of the salvage regimen to the end of the follow-up assessment.
2. Response: lost to follow-up; change in salvage regimen; death. These patients also had confirmed vRNA levels below

200 copies per mL at the end of the follow-up assessment. The time of sustained virologic response was defined as the time from the start of the salvage regimen to the end of the follow-up assessment.

3. Loss of virologic response with persistent low level of viremia: Participants included in this category were those who achieved confirmed vRNA levels <200 copies per mL followed by confirmed levels above this limit (rebound) but <1000 copies per mL; however, the levels did not return to <200 copies per mL.
4. Loss of virologic response with persistent high level of viremia: Participants included in this category were those who achieved confirmed vRNA levels <200 copies per mL followed by confirmed levels above this limit (rebound); however, the levels did not return to <200 copies per mL and had at least 2 measures >1000 copies per mL after the rebound.
5. Nonresponse: Participants included in this category were those who never achieved vRNA levels <200 copies per mL 6 months after beginning the salvage regimen through the end of the follow-up period, and the difference of the median follow-up viral loads minus the baseline viral load was ≤ 1 $\log_{10}$.
6. Partial response: Participants included in this category were those who never achieved confirmed vRNA levels <200 copies per mL 6 months after beginning the salvage regimen through the end of the follow-up period, and the difference of the median follow-up viral loads minus the baseline viral load was ≥ 1 $\log_{10}$.

Genotypic Sensitivity Scores

Each ARV agent in the salvage regimen was assigned a score of 1 if the patient's viral strain was sensitive (ie, if the Stanford HIVdb system total penalty score was 0–29), 0.5 if intermediate (ie, if the total penalty score was 30–59), and 0 if resistant to the drug (ie, if the total penalty score was ≥60). Genotypic Sensitivity Scores (GSS) for the entire regimen was tabulated as the sum of viral sensitivity scores to all agents [19].

Statistical Analyses

Data are reported as absolute values and percentages as well as medians and interquartile ranges (IQRs). The time to the loss of virologic response was defined for patients who had confirmed vRNA levels of <200 copies per mL on 2 consecutive measurements as the time between the start of the salvage regimen and the first consecutive vRNA level recording of more than 200 copies per mL. For patients who never achieved vRNA levels of <200 copies per mL on 2 consecutive measurements, the time to the loss of virologic response was considered 0. Cumulative incidence of loss of virologic response was calculated using all data available as of August 15, 2013 by a competing risks regression analysis [20]. We estimated the cause-specific hazard ratio of various prognostic variables (and its 95% confidence interval) for virologic failure by a competing risks regression modeling. Values were considered significant when $P < .05$.

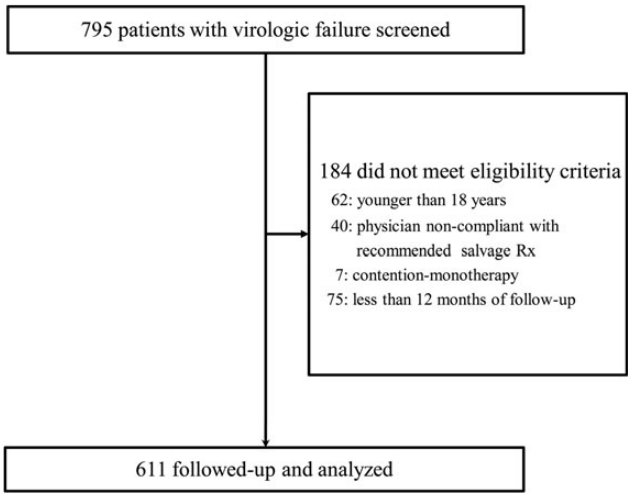

Figure 1. Study profile.

Analyses were performed with Stata software, version 13 (StataCorp, College Station, TX).

Two different approaches were used to handle patients lost to follow-up before August 2013: (1) the observed-failure (OF) approach deemed patients with a documented loss of virologic control as treatment failures; conversely, participants lost to follow-up whose final 2 measurements showed vRNA levels <200 copies per mL were classified as responders; and (2) the noncompleter = failure (NC = F) approach deemed all patients lost to follow-up as having lost virologic control regardless of whether their last 2 measurements showed vRNA levels <200 copies per mL. This study was approved by the Research Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán."

RESULTS

Of the 795 patients experiencing therapeutic virologic failure evaluated by the CORESAR, 611 fulfilled the eligibility criteria and were included in the analysis (Figure 1). The demographic data, clinical features, and prior ARV therapies of this sample are shown in Table 1.

Genotype testing was performed and analyzed for 568 (93%) patients. The results showed the presence of the mutations M184I/V, K65R, 3 or more thymidine-analog mutations (TAM), and the 3 pathway 1 TAM (M41L, L210W, and T215Y) in 74.2%, 9.2%, 52.3%, and 25.5% of these patients, respectively. We identified at least 1 major protease inhibitor resistance-associated mutation (mPI-RAM) in 65.3% of patients, and 3 or more of these mutations were identified in 39.6% of patients; median number of mPI-RAM was 2 (IQR = 0–3).

Table 2 depicts the 10 salvage ARV regimens that were most frequently recommended by the CORESAR. These regimens

Table 1. Baseline Characteristics of the 611 Patients Receiving a Recommended Salvage Regimen

Characteristic	Value
Age (years): Md (IQR)	40 (33–46.5)
Male: *n* (%)	508 (83%)
Time since HIV diagnosis (years): Md (IQR)	12.3 (9–15.2)
Nadir CD4$^+$ T-count (cells/mm^3): Md (IQR)	69.0 (27.0–158.0)
ARV therapy duration (years): Md (IQR)	10.5 (7.6–13.3)
Number of previously used ARV regimens: Md (IQR)	4.0 (3.0–5.0)
Patients with <95% drug adherence: *n* (%)	398 (65%)
Patients without documented plasma HIV-RNA levels below the limit of detection at any time before the recommended salvage regimen: *n* (%)	306 (50%)

Abbreviations: ARV, antiretroviral; HIV, human immunodeficiency virus; IQR, interquartile range; Md, median.

Table 3. Extended-Activity ARVs[a] in Recommended Salvage Regimens

Number of Extended-Activity ARVs	Number of Cases (%)
None	99 (16.2)
1	117 (19.1)
2	232 (38)
3 or more	163 (26.7)
Type of extended-activity ARVs	
Raltegravir	416 (68.1)
Boosted-darunavir	387 (63.3)
Etravirine	223 (36.5)
Enfuvirtide	22 (3.6)
Maraviroc	16 (2.6)
Boosted-tipranavir	11 (1.8)

Abbreviation: ARV, antiretroviral.

[a] Boosted-darunavir, boosted-tipranavir, etravirine, raltegravir, enfuvirtide, and maraviroc.

were prescribed to 67% of the 611 study participants. Table 3 shows the distribution of patients according to the number of XA-ARV included in the salvage regimens. Two or more of these novel drugs were prescribed to 65% of participants. The regimen included a ritonavir-boosted protease inhibitor for the great majority (98.7%) of patients; the 2 most frequently prescribed ritonavir-boosted protease inhibitors were darunavir and lopinavir (in 63% and 29% of cases, respectively). The 2 most frequently prescribed nucleotide reverse-transcriptase inhibitor (NRTI) backbones were tenofovir (± emtricitabine, in 51% of cases) and tenofovir + zidovudine (in 14% of cases); 31% of patients received an NRTI-sparing regimen. Median GSS score of 568 regimens was 3 (IQR = 2.5–3). Two percent, 10.2%, 25.9%, 54.8%, and 7% of these regimens had a GSS score ≤1.5, 2, 2.5, 3, and >3, respectively.

The median follow-up time of the 611 patients was 33 months (IQR = 22–43 months). The patients were distributed according to the outcome definitions as follows: 438 (72%) patients were persistent responders who completed follow-up; 62 (10.1%) patients were persistent responders until the premature end of

Table 2. The 10 Most Frequently Recommended Antiretroviral Salvage Regimens Across 611 Patients

Drug Regimen	Number of Patients (%)
Darunavir/ritonavir + etravirine + raltegravir	112 (18.3)
Darunavir/ritonavir + raltegravir + tenofovir (± emtricitabine or zidovudine)	95 (15.5)
Lopinavir/ritonavir + raltegravir + tenofovir (± emtricitabine)	39 (6.4)
Darunavir/ritonavir + etravirine + tenofovir (± emtricitabine)	36 (5.9)
Lopinavir/ritonavir + raltegravir + etravirine (± emtricitabine)	27 (4.4)
Darunavir/ritonavir + efavirenz + tenofovir (± emtricitabine)	24 (3.9)
Darunavir/ritonavir + raltegravir + efavirenz	23 (3.8)
Darunavir/ritonavir + raltegravir + tenofovir (± emtricitabine)	18 (2.9)
Lopinavir/ritonavir + raltegravir + tenofovir + zidovudine	18 (2.9)
Lopinavir/ritonavir + tenofovir + zidovudine	16 (2.7)
Other	203 (33.3)
Total	611 (100)

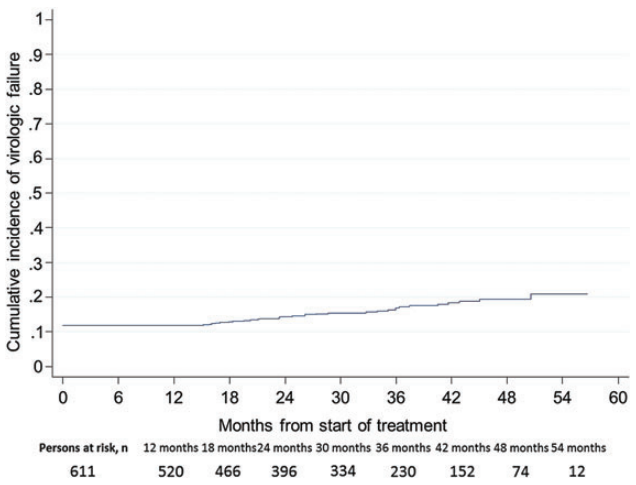

Figure 2. Time to loss of virologic response (111 events). O-F approach. The plot represents 1 minus the probability of remaining event-free as estimated using the competing risks regression analysis. The presented number of events is the total number of events throughout follow-up (57 months).

follow-up (22 dropped out, 20 changed their drug regimens, and 20 died); 13 (2.1%) patients were classified as responders with a loss of virologic control (rebounders) and subsequent low levels of viremia; 18 (3%) patients were classified as responders with loss of virologic control (rebounders) and subsequent high levels of viremia; 67 (11%) patients were nonresponders; and 13 (2.1%) patients were partial responders. After using the OF approach, the cumulative incidences of the loss of viral response were 11.9%, 14.4%, 16.9%, and 19.4% at the 12-, 24-, 36-, and 48-month follow-up assessments, respectively (Figure 2). Applying the NC = F approach, the cumulative incidences of the loss of viral response were 14.7%, 21.4%, 27.7%, and 35.5% at the 12-, 24-, 36-, and 48-month follow-up assessments, respectively.

Of the 531 responders (with or without a subsequent loss of virologic control), the median change in the $CD4^+$ T-cell count (ie, the last measure minus the cell count before the assessment by the CORESAR) was 162 cells per mL (IQR = 45–304 cells per mL). In contrast, for the 80 nonresponders, the median change in the CD4 + T-cell count was −31.5 cells per mL (IQR = −121.3–51 cells per mL). Twenty (3.3%) patients died: 10 (1.8%) responders and 10 (12.5%) nonresponders. Markers of virologic failure are shown in Table 4.

Table 4. Univariate Analysis of Factors Associated With Loss of Virologic Response

	Hazard Ratio (95% CI)	*P* Value
Age (years)		
≤40	1	
>40	0.59 (0.41–0.86)	<.01
Nadir CD4 count (cell/mm^3)		
≥100	1	
<100	1.53 (1.01–2.31)	.04
Baseline CD4 count (cell/mm^3)		
≥200	1	
<200	1.51 (1.05–2.17)	.03
Baseline pVL log_{10}		
<4.4	1	
≥4.4	1.50 (1.04–2.15)	.03
ARV therapy duration (years)		
<10	1	
≥10	0.65 (0.46–0.94)	.02
Number of previously used ARV regimens		
<4	1	
≥4	1.04 (0.73–1.48)	.83
Time since HIV diagnosis (years)		
<12	1	
≥12	0.77 (0.54–1.10)	.16
Genotypic sensitivity score		
≥3	1	
<3	0.73 (0.48–1.10)	.13

Abbreviations: ARV, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; pVL, plasma viral load.

DISCUSSION

Many patients in our study had been exposed to numerous and diverse drug combinations composed of agents from the 3 major classes of ARVs (often with suboptimal therapeutic adherence) over several years. For most of these patients, long periods of ongoing, persistent, detectable viremia under selective drug pressure led to the development of predominant HIV variants with triple-class drug-resistant mutations and intraclass cross-resistance. Thus, in a significant proportion of the patients, a nonsatisfactory therapeutic result using conventional ARVs was expected, and one or more new XA-ARV drugs were needed to construct an effective ARV salvage regimen.

The design of optimally effective salvage regimens in multiple drug-resistant patients is usually a major therapeutic challenge for clinicians. The construction of ARV regimens aimed at achieving full and lasting virologic suppression while minimizing toxicity, inconvenience, and costs is a complex task. A lack of specific clinical decision-making skills can potentially drive regimens toward functional monotherapies with XA-ARVs. In turn, the failure of these new drugs can quickly lead to a loss of activity and even to intraclass cross-resistance, leaving patients with few, if any, options for the future. Thus, expert advice is critical in settings such as the majority of HIV clinics in Mexico.

In 2008, an expert advisory board was created to use the new XA-ARVs cost effectively and rationally. The task of this committee has been to regulate the prescription of these drugs (no prescription is allowed without the authorization of this advisory board) by recommending the best possible salvage regimen to clinicians caring for patients with extensive ARV experience and detectable viremias in their current treatment.

A longitudinal analysis of a cohort of 611 patients whose physicians received advice from this committee showed satisfactory outcomes. These results were similar to those reported in clinical trials of patients infected with multiclass-resistant HIV strains [13]. After a median follow-up period of 33 months (25% of patients had follow-ups of 43 months or longer), 82% of patients achieved a lasting vRNA level of <200 copies/mL, and a partial virologic suppression (ie, a viral load decline >1 log_{10}) was observed in 2% of patients. Among responders (regardless of loss of virologic control), a median rise of 162 cells per mL was registered with regard to the $CD4^+$ T-cell counts; 25% of these patients achieved an increase of at least 300 cells per mL. Thus, the adverse natural course of HIV infection was likely improved by halting immunologic deterioration and preventing clinical progression, in approximately 80% of these individuals.

Several possible explanations exist for these encouraging outcomes.

1. The members of the advisory board are senior clinicians (internists or infectious diseases specialists) who work in highly

esteemed academic public health institutions and with a minimum of 5 years of experience in HIV patient management. Most of these physicians have long-standing backgrounds in research and postgraduate medical training.

2. The optimal salvage regimen was constructed to have a high probability of achieving maximal HIV replication suppression. The panel continuously retained the goal of recommending an ARV combination containing 3 fully active drugs whenever possible. When these drugs were unavailable, they recommended at least 2 agents with complete activity associated with one or more partially active drugs. The core of the great majority of regimens was a boosted protease inhibitor (a class of agents with a high genetic barrier to resistance).
3. The positive attitudes held by the majority of physicians who were in strong compliance with the experts' advice and the recommended drug regimens.
4. A favorable behavioral change could have occurred among patients. Although patient compliance to the new salvage regimens was not systematically measured, it is likely that a significant proportion of patients greatly improved their adherence because durable viral control requires optimal drug compliance. This result occurred despite the fact that the great majority of individuals in our study had a background of poor compliance. Additional qualitative research is needed to understand the determinants of this change, including the active role that the physicians played in promoting it.

Among the patients in our study, the use of optimized, highly effective salvage regimens led to (in most cases) a reversal of the predicted unfavorable clinical prognoses. Consequently, an intervention such as ours might significantly reduce the morbidity and healthcare costs that stem from the incidence of acquired immune deficiency syndrome (AIDS)-related events, hospitalizations, functional monotherapies with XA-ARV, and the transmission and dissemination of MDR-HIV strains in the community.

CONCLUSIONS

The current paper describes the success of a strategy aimed at the prudent use of ARVs based on a collaborative alliance between medical academic settings and the governmental offices in charge of programs seeking to control the HIV/AIDS epidemic. Our experience is unique in the literature and can serve as an example to other countries.

In summary, a strategy based on the therapeutic decision making of physicians who care for patients infected with MDR-HIV was successful. In routine practice, the rate of patients with extensive treatment experience achieving the maximal virologic control with an optimized salvage regimen (recommended by a peer advisory committee) was comparable with that of achieving virologic control in controlled clinical trials examining novel XA-ARVs.

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Author contributions. J. J. C. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

J. J. C., J. S.-M., and L. E. S.-R. contributed to study concept and design. J. J. C. and P. A.-S. acquired data. J. J. C. and P. A.-S. contributed to analysis and interpretation of data. J. J. C. drafted the manuscript. J. J. C., J. S.-M., L. E. S.-R., and P. A.-S. critically revised the manuscript. J. J. C. contributed to statistical analysis.

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Potential conflicts of interest. J. J. C. has served as a consultant on advisory boards for Janssen Pharmaceutical and reports personal fees from MSD. J. S.-M. reports grants from Pfizer and personal fees from Janssen Pharmaceutical, MSD, ViiV Healthcare, and Gilead. L. E. S.-R. reports personal fees from Abbott/Abbvie, Merck, BMS, Roche, Roche Diagnostics, Abbott Diagnostics, Janssen Pharmaceutical, and GlaxoSmithKline.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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